Thrombosis Research 149 (2017) 48–55

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Management of distal deep vein thrombosis☆

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ARTICLE INFO

Article history:
Received 22 September 2016
Received in revised form 7 November 2016
Accepted 9 November 2016
Available online 10 November 2016

Keywords:
Calf deep vein thrombosis
Distal deep vein thrombosis
Diagnosis
Anticoagulant therapy
Compression ultrasound

ABSTRACT

Isolated distal deep vein thrombosis (DVT), also known as calf DVT, represents up to 50% of all lower limb DVT in ultrasound series and is therefore a frequent medical condition. Unlike proximal DVT and pulmonary embolism (PE), which have been extensively studied and for which management is well standardized, much less is known on the optimal management of isolated calf DVT. Recent data arising from registries and non-randomized studies suggest that most distal DVTs do not extend to the proximal veins and have an uneventful follow-up when left untreated. This data had some impact on the international recommendations which recently stated that ultrasound surveillance instead of systematic therapeutic anticoagulation might be an option for selected low-risk patients. However, robust data arising from randomized studies are scarce. Indeed, only five randomized trials assessing the need for anticoagulation for calf DVT have been published. Many of these trials had an open-label design and were affected by methodological limitations. The only randomized placebo-controlled trial included low-risk patients (outpatients without cancer or previous venous thromboembolic events (VTE)) and was hampered by a limited statistical power. Nevertheless, data from this trial tend to confirm that the use of therapeutic anticoagulation in low-risk patients with symptomatic calf DVT is not superior to placebo in reducing VTE, but is associated with a significantly higher risk of bleeding. Further randomized studies are needed to define the best therapy for high-risk patients (inpatients, patients with active cancer or previous VTE), and the optimal dose and duration of treatment.

Contents

☆ This manuscript represents original work, and it is not under consideration for publication elsewhere. It has never been neither submitted nor published in another scientific journal. All authors meet criteria for authorship and none of the authors have any conflict of interest. All had access to all data in the study, read, approved the final manuscript, and held responsibility for the decision to submit it for publication.

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http://dx.doi.org/10.1016/j.thromres.2016.11.009
0049-3848/

1. Introduction

Isolated distal deep vein thrombosis (DVT), i.e. infra-popliteal DVT without extension to proximal veins (popliteal vein or above) or pulmonary embolism (PE), also known as calf DVT, is frequent and represents 30% to 50% of all lower limb DVT diagnosed on ultrasound series [1–3]. Unlike proximal DVT and PE, which have been extensively studied and for which management is well standardized and the subject of high-level evidence and recommendations, much less is known on the optimal management of isolated distal DVT [4].

The rate of extension to the proximal veins, as well as the rate of PE associated with distal DVT is highly variable from one study to the other. As a result, there is significant variation in diagnostic and therapeutic practices across centers [1,5–8]. In some centers, both the proximal veins and the calf veins are imaged in all patients with suspected DVT, and patients diagnosed with isolated calf DVT are treated with anticoagulant therapy [9]. Other centers rely on serial imaging of the proximal veins only, and thus do not diagnose or treat calf DVT [10]. In the latter strategy, in case of a negative proximal ultrasound, the test is often repeated one week later to rule out extension of a calf DVT to proximal veins. Comparisons between these two diagnostic strategies have shown that the proportion of patients diagnosed with DVT and thus treated with anticoagulants was higher when using whole-leg imaging as compared with serial proximal imaging. Nevertheless, diagnosing and treating distal DVT was not associated with better overall safety for patients. Indeed, the three-month venous thromboembolism (VTE) risk was equivalent in patients left without treatment based on either strategy [11,12]. These results thus question the need to systematically diagnose and treat all calf DVT with anticoagulants, particularly in patients free of any of the major strong identified predictors of DVT extension/recurrence (inpatients, patients with history of previous VTE or with cancer), who represent the majority of calf DVT patients [4,13,14].

The aim of this review is to discuss the therapeutic management of symptomatic isolated distal DVT. Because of lack of extensive data on this specific subject, and in order to better understand some important issues, the natural history of distal DVT and limitations in the accuracy of its diagnosis are presented first. Then, the most recent available studies on distal DVT treatment as well as international recommendations are discussed.

2. Epidemiology and natural history of distal DVT

In studies including inpatients, 80% of all diagnosed DVT are proximal DVT and 20% are calf DVT [15–17]. However, some studies including outpatients diagnosed with DVT by compression ultrasound (CUS) report a proportion of calf DVT as high as 60 to 70%, underlining the potential relevance of the problem in everyday clinical practice [18,19].

The natural history of DVT 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 pattern of thrombus extension [17]. Whereas the embolic potential of proximal DVT is unanimously recognized, distal clots appear to have a much lower embolic potential, although data remain limited [20]. Therefore, the rate of extension of distal DVT to the proximal veins as well as the rate of PE are crucial issues as they largely determine the clinical significance of distal DVT in terms of patients' outcomes, and hence in terms of need for treatment.

2.1. Assessing the risk of proximal extension without treatment

Performing a thorough estimation of the risk of extension of distal DVT to proximal DVT and/or PE remains difficult. Indeed, the rate of extension among different studies is highly variable due to high heterogeneity in patients' population, clinical settings and diagnostic strategies.[2,21] Comparison between studies is also limited by disparity in treatment regimens as well as major differences in the follow-up and definition of outcomes (symptomatic extension versus extension diagnosed on systematic testing).

An interesting approach to assess the rate of extension of distal DVT to the proximal veins is to use data arising from diagnostic studies based on serial proximal CUS (described in detail in the next section). These studies show a low rate of proximal DVT (1% to 5.7%) detected by the repeated proximal CUS in patients left untreated after a first negative CUS limited to proximal veins (Table 1) [22–27]. Of note, these studies mainly include outpatients with suspected DVT, so the rather low reported rates of extension to proximal veins could reflect the natural history of untreated calf DVT in a group "low risk" patients.

2.2. Clinical outcomes of patients treated with anticoagulants for distal DVT

Two registry-based analyses aimed to assess patients' outcomes after a symptomatic distal DVT and identified 933 and 1885 eligible patients respectively. As the vast majority of patients included in these French (OPTIMEV) [3] and International (RIETE) [28] registries received therapeutic anticoagulation (97% and 89% respectively), these studies could not add knowledge on the true natural history of distal DVT. Nevertheless, they revealed interesting findings on some differences between patients treated for distal and proximal DVT. The three-month VTE rate was similar in distal and proximal DVT patients. However, mortality was significantly higher in patients with proximal DVT versus distal DVT in both studies (8% vs 4.4% in OPTIMEV and 7.5% vs 2.7% in RIETE). In distal DVT patients, mortality was non-VTE related in the majority of cases. Interestingly, distal DVT was found to be more often associated with transient risk factors (such as recent travel, hospitalisation and recent surgery) than proximal DVT.

The long-term outcome after stopping treatment in patients' prescribed therapeutic anticoagulation for distal DVT was analyzed in two recent prospective observational studies. The first study consisted of a 3-year follow-up of patients included in the OPTIMEV registry. It showed that after treatment cessation, patients with distal DVT ($n = 490$) had a lower annualised rate of overall VTE recurrence compared to patients with proximal DVT (2.7% vs 5.2%, $p = 0.02$), but a similar rate of PE (0.9% vs 1%, $p = 0.83$). Some predictors of recurrence in patients with index distal DVT were identified: age > 50 years, unprovoked event and multiple distal vein involvement [13]. The second study was a single-centre small study ($n = 90$) assessing 2-year outcomes after stopping therapeutic anticoagulation for distal DVT. Treatment duration was of 30 days and 3 months in patients with provoked and unprovoked distal DVT respectively. In this study, male sex and the presence of cancer were associated with higher VTE recurrence rates after treatment cessation, whereas location and the provoked character of the index distal DVT were not [29].

2.3. Comparison of patients' outcomes between treated and untreated patients

Variations in study design and target populations are too large to allow a clinically relevant pooled estimate to compare the proportion of patients with distal DVT who extend to proximal DVT between treated and untreated patients. Nevertheless, a systematic review published in 2006 reported an estimated rate of extension of 10% (95% CI: 7–12%) in untreated patients and of 4% (95%CI: 3–6%) in treated patients [2].

A recent systematic review published this year, including prospective cohort studies and some of the most recent randomized studies, reported an overall proximal extension rate varying between 0% and 35%, corresponding to a mean extension rate of 9%. Although the true signification of a mean value in view of the large heterogeneity of studies can be debated, it helps to give a rough idea of the potential range of extension rate. The reported rate of PE ranged from 0% to 5.8% with a mean rate of 1.4%. None of the available studies found that anticoagulant treatment was associated with a reduction in adverse outcomes. In terms of bleeding, the major bleeding rate (excluding an older study

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

Source, year	Patients (n)	Prevalence of DVT (%)	Proportion of proximal DVTs detected by the 2nd CUS % (95% CI)	Three-month thromboembolic risk, % (95% CI)[a]
Birdwell et al. [23], 1998	405	16	2 (0.8–4.2)	0.6 (0.1–2.1)
Cogo et al. [10], 1998	1702	24	0.9 (0.3–1.2)	0.7 (0.3–1.2)
Bernardi et al. [22], 1998	946	28	5.7 (1.9–12.8)	0.4 (0–0.9)
Wells et al. [27], 1997	593	16	1.8 (0.3–5.2)	0.6 (0.1–1.8)
Perrier et al. [26], 1999	474	24	N.A.*	2.6 (0.2–4.9)
Kraaijenhagen et al. [25], 2002	1756	22	3 (1.9–5.2)	0.7 (0.3–1.6)
Pooled estimate	5876	23	N.A.	0.6 (0.4–0.9)

Abbreviations: DVT: deep vein thrombosis; CUS: compression ultrasonography; N.A.: not applicable.
N.A*: 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.
[a] During 3-month follow-up in patients left untreated after normal proximal compression ultrasonography.

who showed a high major bleeding rate of 7%) was of 0% to 2.1% in patients treated with anticoagulants, whereas no major bleeding was reported in patients who did not receive anticoagulant treatment [21].

All these elements highlight the uncertainty about the natural history of distal DVT, its clinical significance and the need for its treatment and modality and duration of treatment. The increasing occurrence of this medical condition since the implementation in many vascular laboratories of systematic whole-leg compression ultrasound in all patients with suspected DVT has led to considerable efforts over the last 10 to 15 years to answer the question on the need for its treatment with anticoagulants, without any definitive conclusion but with some important data on the potential necessity to stratify the risk of extension in patients with distal DVT to guide decision on treatment. In view of the uncertainty regarding the necessity to treat distal DVT, the question of the necessity to diagnose distal DVT can be raised. As the diagnostic management of distal DVT varies as widely as its therapeutic management among centers, this issue is discussed first in detail the next section. Then, the most recent studies comparing outcomes between treated and untreated patients will be discussed in a dedicated section.

3. Different lower limb venous ultrasound strategies for suspected DVT

Distal or calf DVT involves infra-popliteal veins: posterior tibial veins, peroneal veins, anterior tibial veins, and muscular calf veins (soleus or gastrocnemius veins). The sensitivity and specificity of compression ultrasound (CUS) for proximal DVT are high (97% and 98%, respectively) [30] and the necessity for treating proximal DVT by anticoagulants is widely accepted [31]. On the other hand, the sensitivity and specificity of CUS for distal DVT are lower [15,30]. A meta-analysis by Kearon et al. reported sensitivity of 50% to 75% and specificity of 90% to 95% [30]. Even if another more recent meta-analysis published in 2005 suggested similar values for ultrasound accuracy for calf thrombosis [32], one must take into account that some studies in the hands of highly skilled ultrasonographers using the best ultrasound machines reported much higher values of sensitivity and specificity at the calf level [33]. The improvement in ultrasound technology and increased experience in the field have led to a quite reliable diagnosis of distal DVT in experienced hands when the most reliable diagnostic criterium is used, i.e. the lack of compressibility of a venous segment. However, despite such technologic improvements, some other limitations are still present at the calf level. For example, the rate of inconclusive diagnostic tests has been reported to be as high of 50% in some series (Table 2) [34–37]. This rate might not be true for outpatients in whom calf examination is usually easier, but seems to reflect the reality of inpatients, especially after orthopaedic surgery or in the intensive care unit setting.

3.1. Serial proximal CUS

The limited performances of distal venous examination reported in some studies may explain why many centers use only proximal CUS, i.e. limited to the popliteal, and supra-popliteal veins. Since such protocols do not search for distal DVT (that if present could potentially extend to the proximal veins with a significant risk of PE), the standard diagnostic approach consists of performing a second CUS limited to the proximal veins at day 7, the so-called "serial proximal CUS strategy". Patients with a proximal DVT on the initial CUS are treated with anticoagulants. When the initial examination is negative, patients are not given anticoagulants, and a second proximal CUS is repeated one week later to detect the possible extension of distal DVT. Patients with a second normal CUS are considered as definitely not having a DVT and are not anticoagulated.

Many prospective well designed outcome studies have shown the safety of proximal CUS integrated in diagnostic strategies (Table 1). The six studies used CUS limited to proximal veins [10,22,23,25–27]. Five of these studies used the classical serial proximal CUS and one used a single proximal CUS included in a strategy associating pre-test clinical probability and D-dimer measurement [26].

The pooled estimate of the 3-month thromboembolic risk of these prospective management studies using CUS limited to proximal veins was 0.6 (95% CI: 0.4–0.9%). There was no significant difference in the 3-month thromboembolic risk between these six studies. If one considers each study individually, the 3-month thromboembolic risk in patients with a negative proximal CUS was low: it was lower than 1% in the studies using serial proximal CUS [10,22,23,25,27] (CUS repeated after 1 week in patients with an initially negative CUS) and 2.6% (95% CI: 0.2–4.9%) in the one study that used clinical probability, D-dimer and a single proximal CUS (Table 1) [26]. This compares favourably with the 3-month thromboembolic risk in patients with clinically suspected DVT left untreated after a negative venogram (the gold standard), which was found to be 1.9% (95% CI 0.4–5.4%) [38].

Even if serial proximal CUS is very safe, its main limitation is the need for a second ultrasound examination, which is cumbersome, costly and has a very low yield as it reveals a proximal DVT in only 1% to 5.7% of patients (Table 1).

3.2. Single complete (proximal and distal) CUS

Seven prospective outcome studies using a single complete (i.e. proximal and distal) CUS have been published (Table 3) [11,33,39–43]. Patients were treated if CUS showed a proximal or distal DVT and were left untreated if proximal and distal veins were normal, without any further testing. These studies showed that extending the ultrasonographic

Table 2
Rate of indeterminate calf ultrasound examinations.
Adapted from reference [35].

First author	Study type	Frequency of indeterminate examinations %, (n/n)
Rose et al. [36], 1990	Prospective	42% (21/50)
Simons et al. [37], 1995	Prospective	29% (16/56)
Atri et al. [34], 1996	Prospective	9.3% (10/108)
Gottlieb et al. [35], 1999	Retrospective	82.7% (8206/249)
Pooled Total	–	54.6% (253/453)

Table 3
Performances and safety of a single complete (proximal and distal) compression ultrasonography for diagnosing DVT in management outcome studies.

Source, year	Patients (n)	Prevalence of all DVT n (%)	Distribution of DVT level n (%)		Three-month thromboembolic risk % (95% CI)[a]
		All	Proximal	Distal	Single proximal and distal CUS
Elias et al. [33], 2003	623	204 (33)	112 (55)	92 (45)	0.5 (0.1–1.8)
Schellong et al. [39], 2003	1646	275 (17)	121 (44)	154 (56)	0.3 (0.1–0.8)
Stevens et al. [40], 2004	445	61 (14)	42 (69)	19 (31)	0.8 (0.2–2.3)
Subramaniam et al. [41], 2005	526	113 (22)	49 (43)	64 (57)	0.2 (0.01–1.3)
Bernardi et al. [11], 2008	1053	278 (26)	213 (76)	65, (24)	1.2 (0.5–2.2)
Sevestre et al. [43], 2009	3871	1023 [26]	454 (44)	569 (56),	0.6 (0.3–1.2)
Sevestre et al. [42], 2010	1926	395 (21)	155 (39)	240 (61)	0.6 (0.1–1.7)
Pooled estimate	10′090	2349 [23]	1146 [49]	1203 (51)	0.6 (0.3–0.9)

[a] During 3-month follow-up in patients left untreated after a normal complete (proximal and distal) compression ultrasonography. Abbreviations: NA: not applicable; DVT: deep vein thrombosis; CUS: compression ultrasonography.

examination to distal veins without repeating the CUS at one week is very safe. Indeed, the pooled estimate of the 3-month thromboembolic risk performed in a systematic review and meta-analysis is of 0.6 (95% CI: 0.3–0.9%) [9].

However, in spite of their diagnostic safety, these studies point to some important problems. First, such an approach is costly and time-consuming as complete CUS is proposed to all patients with suspected DVT. Indeed, in outpatients with clinically suspected DVT, a normal Enzyme Linked Immuno-adsorbent Assay (ELISA) D-dimer test allows to withhold anticoagulation without further testing in about one third of outpatients at a much lesser expense and with a similar safety [26]. Second, the pooled estimate of the 3-month thromboembolic risk of these studies is similar to that computed for studies using a strategy including proximal CUS (Table 1 and Table 3). This means that detecting calf DVT may actually be deleterious: it does not reduce the 3-month thromboembolic risk and it entails a risk of unnecessary anticoagulant treatment in patients who would have fared well without anticoagulant treatment. Moreover, because of the limitations in the diagnostic performance of CUS at the calf level, some of the positive findings might even be false positives, rendering the potentially unnecessary exposure to bleeding risk associated with anticoagulation even more unacceptable. To give an idea of the potential extent of this issue, a pooled analysis of the studies performing complete CUS shows that among a total of 10,090 included patients, 1203/2343 (51%) of diagnosed DVT were distal DVT (Table 3). This could mean that in half of patients with suspected DVT undergoing complete CUS with a final positive diagnosis of DVT, we are not certain to do more good or harm to the patient by diagnosing the (distal) DVT.

3.3. Serial proximal versus single complete (proximal and distal) CUS in suspected DVT

The next logical step was obviously to perform a direct comparison between serial proximal CUS and single complete CUS diagnostic strategies for DVT. This was performed in three studies, with very similar results [11,12,44]. Therefore, only the most robust study in terms of methodology will be discussed here [11].

In this prospective randomized multicenter trial, a strategy including serial two-point (femoral and popliteal) proximal CUS associated with D-dimer testing was compared to a single whole leg CUS strategy in >2,000 outpatients with a clinical suspicion of DVT (Table 4) [11]. In the proximal CUS arm, patients with a normal two-point-CUS underwent qualitative D-dimer testing (SimpliRED®, Agen Biomedical, Australia). Patient with negative D-dimer were spared further investigations and not treated with anticoagulants. Only patients with abnormal D-dimer levels underwent the repeat CUS at one week. Both strategies reported similar 3-month rate of VTE: 0.9% (95% CI 0.3–1.8%) for the two-pointproximal-CUS and D-dimer arm versus 1.2% (95% CI 0.5–2.2%) for the complete single CUS arm. The safety of both strategies was therefore similar. It should be noted that 23% (65/278) of patients with confirmed DVT in the complete CUS arm were treated with an anticoagulant for a distal DVT, without decreasing the 3-month thromboembolic risk. Authors thus concluded that detecting isolated distal DVT might not be as relevant as previously believed and that the search for distal DVT might even expose patients to the harm of unnecessary anticoagulant treatment.

The advantages and disadvantages of using serial proximal CUS versus a single complete CUS are summarized in Table 5.

To decrease the number of patients undergoing a distal vein examination, a new diagnostic strategy was recently evaluated in a prospective outcome study. All patients with suspected DVT had a clinical probability assessment. Patients with suspected DVT had a whole leg CUS (i.e. proximal and distal) only in case of both a likely clinical probability *and* a positive D-dimer measurement. Patients with an unlikely probability and negative D-dimer did not undergo CUS and were left untreated. All other patients with positive D-dimer result had a single proximal CUS only. The overall prevalence of DVT was of 18% in the whole cohort. Among all confirmed DVTs, 39% were isolated distal DVT, which is lower than the pooled estimate of 51% in studies including complete CUS for all patients (Table 3). In spite of a lower rate of detection of distal DVT, this strategy revealed to be safe, with a three-month thromboembolic risk of 0.9% (95% CI, 0.44–1.70) [45].

4. D-dimers in the diagnosis of distal DVT

The safety and the cost-effectiveness of D-dimer measurement in the diagnosis of patients with suspected DVT has been extensively studied. D-dimer measurement has been proven to be highly sensitive but not very specific for the presence of venous thromboembolism, and to be associated with a very high negative predictive value for DVT in different patient populations [26,46,47].

D-dimer seems to have a lower sensitivity and a lower negative predictive value for calf DVT than for proximal DVT. For example, Jennersjö and coworkers reported that as many as 35% of patients with calf DVT may have normal D-dimer levels, suggesting a limited sensitivity of the test to rule out distal DVT [48]. However, some other studies reported much higher values of sensitivities [49,50], rendering a robust evaluation of D-dimer sensitivity for distal DVT quite difficult. Nevertheless, a

Table 4
Main results of the randomized trial comparing serial 2-points proximal CUS with a single complete CUS in patients with suspected DVT [11].

	Serial 2-points proximal CUS	Single complete CUS
Patients (n)	1045	1053
DVT [n (%)]	231 (22.1)	278 (26.4)
Proximal (n)	231	213
Distal (n)	0	65
3-months VTE risk [% (95% CI)]	0.9 (0.3–1.8)	1.2 (0.5–2.2)

Adapted from Bernardi et al. [11].
CUS, complete compression ultrasound; DVT, deep vein thrombosis.

Table 5
Advantages and disadvantages of serial proximal CUS and single complete CUS.

	Advantages	Disadvantages
Serial proximal CUS	Safety in terms of 3-month VTE risk No risk of overtreatment Easy to perform Short (3–4 min) Few inconclusive tests	Repeated testing
Single complete CUS	Safety in terms of 3-month VTE risk Stand-alone test	Risk of overtreatment More difficult to perform Longer (12–14 min) to perform More inconclusive tests in inpatients Lower diagnostic performances

meta-analysis showed that all D-dimer assays had a higher sensitivity for proximal than distal DVT: 98% vs. 86% for ELISA test, 94% vs 79% for latex agglutination and 84% vs 64% for whole-blood agglutination tests [51]. A more recent study reported that the area under the curve (AUC) of the receiving operating characteristic (ROC) analysis for D-dimer and calf DVT was of 0.72 [52].

Altogether, these data suggest that D-dimer are indeed less sensitive at the distal than at the proximal level, and that some patients may have a distal DVT and D-dimer levels below the usual cut-off value set at 500 ng/ml. However, one should rather keep in mind that in terms of patients' outcomes, many prospective outcome studies including several thousands of patients have clearly shown that patients with suspected PE or suspected DVT have a very low three-month thromboembolic rate (<1%) when left untreated on the basis of a negative D-dimer test [53]. Another important point is that in the studies assessing the accuracy of D-dimer for distal DVT, the reference diagnosis test was ultrasound. Due to the imperfect accuracy of CUS itself at the distal level, some of the detected thrombi might also have been false positive results of ultrasound testing rather than false negative results of D-dimer, limiting a thorough assessment of D-dimer performance in diagnosing distal DVT. Therefore, we still believe the fear of calf DVT should not alter the full confidence in a normal D-dimer test result to identify patients who will have very favorable outcomes without anticoagulant treatment. Interestingly, a similar discussion may also be held for isolated subsegmental PE. Indeed, whereas D-dimer sensitivity is estimated at around 75% for subsegmental PE even for highly sensitive tests, [54] a negative D-dimer test result has been shown to be very safe to exclude PE in outcome studies by identifying patients at very low risk of 3-month thromboembolic events without treatment.

As a general consideration, the uneventful outcome of patients left untreated after a negative D-dimer, even though small clots (distal DVT or subsegmental PE) may be "missed" by such a test, further advocates for the doubt about the necessity to treat all distal DVTs.

5. Recent trials and recommendations for therapeutic management of distal DVT

5.1. The first randomized trials assessing the need for anticoagulant treatment

To date and to our knowledge, only 5 randomized trials have assessed the need for anticoagulant treatment in patients with calf DVT [14,55–58], four of which have been published to date and will be discussed here. The results of the fifth study, the only double-blind randomized placebo-controlled study in this field, will be presented and discussed in detail in a dedicated section.

The first study was published more than thirty years ago by Lagerstedt and coworkers [56]. Though the landmark study in the field, it was a small, open-label study with many methodological limitations. After a 10-day course of therapeutic heparin, 51 patients were randomized to receive either therapeutic warfarin (target INR 2–3) or no warfarin. During the three-month follow-up, no patient in the warfarin arm had a recurrent event, while 19/28 patients who did not receive warfarin had recurrent VTE events. However, recurrent events were assessed by physical examination and serial isotopic tests, which were later abandoned due to their limited sensitivity. It is therefore quite difficult to rely on this single study to recommend systematic anticoagulation for all distal DVTs. Nevertheless, it is interesting to point out that on the basis of this single trial and due to the absence of other randomized data, the 2008 ACCP consensus still recommended to treat all calf DVTs with a three-month course of anticoagulant treatment (Grade 2C) [59].

In another open-label, randomized trial, Pinede et al. compared a 6-week against a 12-week course of oral anticoagulant treatment in patients with symptomatic DVT [57]. Among the group of patients with distal DVT ($n = 197$ patients), those who received 6 weeks of treatment had both less recurrent events (2.0% vs 3.4%, relative risk 0.58 (95% CI:0.1–3.36)) and less major bleedings (1.0% vs 3.4%, relative risk 0.29 (0.03–2.72)) compared to those who received 12 weeks of treatment. Despite an open-label design, the study suggested that 6 weeks of treatment are probably enough for distal DVT.

One randomized study focused on patients with calf muscle vein thrombosis only, i.e., soleus or gastrocnemius vein thrombosis [58]. This study, which was not placebo-controlled, randomized patients to receive either 10 days of subcutaneous injections of therapeutic dose of the low molecular weight heparin (LMWH) nadroparin associated with elastic compression or elastic compression alone. The study did not show significant differences in the rate of extension to proximal veins nor in the recanalization rate of affected venous segments between the two groups.

A fourth randomized open-label feasibility study compared therapeutic anticoagulation with the LMWH dalteparin followed by warfarin to a conservative treatment (non-steroidal anti-inflammatory drugs and/or paracetamol) in patients with calf DVT [55]. A total of 70 patients were randomized, and while no patients in the anticoagulation arm had a VTE event, 4 out of 35 patients (11.4%) of those in the conservative treatment arm had a thromboembolic event. However, the small sample size and the open-label design limit the robustness of conclusions that could be drawn from this study.

Altogether, the analysis of these available randomized data shows a high disparity between reported results, and does not allows drawing firm conclusions.

5.2. Evolving international recommendations for the treatment of distal DVT

Nevertheless, some reassuring data published in these randomized trials and also in non-randomized trials has probably had some impact on the recommendations included in international expert consensus guidelines such as those established by the American College of Chest Physicians (ACCP). As an example, a cohort study published in 2010 including 431 non-consecutive outpatients in two Italian centers showed a low rate of proximal extension or thromboembolic events in patients left untreated for a distal DVT [60]. In a more recent study, 171 patients diagnosed with distal DVT were treated with twice-daily administration of therapeutic LMWH for 1 week, followed by half-dose LMWH for another 3 weeks [61]. During the treatment period, 5 patients (2.9%) had a proximal extension. Further recurrences during the rest of 3-month observation period, occurred in only 4 patients, three of whom in patients with an index unprovoked event, suggesting that prolonged full dose therapeutic treatment might not be necessary for all patients with calf DVT.

All these rather reassuring data had probably some impact on the last ACCP recommendations [4,62], that contrary to the suggestions of

2008, now suggest that serial imaging of the deep veins for two weeks could be proposed over initial anticoagulation in patients without severe symptoms or risk factors for extension. The presence of the risk factors listed in Table 6 should warrant therapeutic anticoagulation according to these recommendations.

5.3. Is it safe not to treat distal DVT in low risk patients?

The next step to improve the management of distal DVT was probably to assess the safety of not giving anticoagulant treatment to selected patients with distal DVT at low risk of proximal extension and of thromboembolic events. This was the basis to draft the CACTUS trial, which is the only randomized placebo controlled study in the field of distal DVT [14]. In the CACTUS trial, 259 outpatients without active cancer or previous VTE were assigned to receive once daily subcutaneous injections of either the LMWH nadroparin, at the dose of 171 UI/kg, or placebo for six weeks. The primary efficacy outcome measure was the composite of extension of calf DVT to proximal veins, contralateral proximal DVT or PE at six weeks. The primary safety outcome measure was major or clinically relevant non-major bleeding at 6 weeks. All patients were also prescribed elastic compression stockings for 6 weeks and followed for 90 days.

The primary efficacy outcome occurred in 4 of 122 patients (3.3%) in the nadroparin arm and in 7 of 130 patients (5.4%) in the placebo arm ($p = 0.54$; risk difference −2.1% (95% CI: −7.8 to +3.5%)). Major or clinically relevant non-major bleeding occurred in 5 of 122 patients (4.1%) in the nadroparin arm and in 0 of 130 patients (0.0%) in the placebo arm ($p = 0.03$; risk difference +4.1 (95% CI: +0.4 to +9.2%)) (Table 7). In the nadroparin arm, 1 patient died from metastatic cancer and 1 patient was diagnosed with type II heparin induced thrombocytopenia. The main conclusions of the study were that the use of therapeutic doses of nadroparin for six weeks in low-risk outpatients with symptomatic calf DVT was not superior to placebo in reducing the risk of proximal extension or thromboembolic events, but was associated with a significantly higher risk of bleeding. The main limitation of the study is that the target sample size was not reached, resulting in limited statistical power.

In a recent monocentric non-randomized study including 384 patients with calf DVT, in which the decision to give anticoagulant treatment was retrospectively analyzed by the investigators, 243 patients were treated with anticoagulants and 141 patients were not. Interestingly, anticoagulation was associated with a non-significant reduced adjusted odds ratio (OR) of developing PE 0.37 (95% CI: 0.09 to 1.45), which were mainly lobar or segmental. However, anticoagulant treatment was associated with a 4.87 (95% CI: 1.37 to 17.39) adjusted OR to develop bleeding. Of note, a high proportion of these patients were inpatients (71% in the non-treated group and 49% in the treated group). So even though the OR have been adjusted for age, sex, care setting at the time of calf DVT, existing cancer and history of DVT to compare treated and untreated patients, the overall population is a rather high risk population of patients [63].

Altogether, these studies question the necessity to treat all calf DVT with therapeutic anticoagulation. Due to the frequency of distal DVT (calf DVT represents approximately half of all diagnosed DVTs in ultrasound series), avoiding systematic anticoagulation could have a significant impact for the individual patient and from a public health perspective.

Table 6
Risk factors for calf DVT extension warranting anticoagulation according to ACCP recommendations [4,62].

Positive D-dimer
Extensive thrombosis or close to the proximal veins (>5 cm in length, involves multiple veins; >7 mm in maximum diameter)
No reversible provoking factor for DVT
Active cancer
History of VTE
Inpatient status

Table 7
Major efficacy and safety outcomes at day 42 in the CACTUS trial [14].

	Therapeutic nadroparin ($N = 122$)	Placebo ($N = 130$)	Absolute risk difference, %, (95% CI)	p value
Primary outcome by day 42	4 (3.3%)	7 (5.4%)	−2.1 (−7.8 to +3.5)	0.54
Proximal DVT	2 (1.6%)	7 (5.4%)	–	–
Pulmonary embolism	2 (1.6%)	0 (0.0%)	–	–
Major bleeding or non-major clinically relevant bleeding	5 (4.1%)	0 (0.0%)	+4.1 (+0.4 to +9.2)	0.03
Major bleeding	1 (0.8%)	0 (0.0%)	–	–
Non-major clinically relevant bleeding	4 (3.3%)	0 (0.0%)	–	–

5.4. Elastic compression stockings (ECS) in distal DVT

Elastic compression stockings (ECS) are usually prescribed in patients with confirmed DVT, with the aim of reducing pain and edema in the acute phase and reducing the risk of post-thrombotic syndrome (PTS). PTS refers to chronic clinical symptoms and signs of venous insufficiency after a DVT, resulting from persistent venous occlusion and/or valvular dysfunction and reflux. The risk of developing PTS is higher in case of proximal and especially ilio-femoral DVT, ipsilateral recurrence, residual vein obstruction, obesity and pre-existing venous insufficiency [64].

Whereas previous international guidelines recommended systematic prescription of ECS for two years in all patients with acute proximal DVT [4], the true benefit of ECS to prevent PTS has recently been questioned after the publication of the SOX trial [65]. The relationship between isolated calf DVT and PTS is not well established, and is currently under study (NCT00421538). Nevertheless, in clinical practice, patients seem to benefit from elastic compression during the initial phase after diagnosis to reduce pain and edema. The need to prescribe ECS for a longer duration after calf DVT is not supported by evidence.

6. Conclusions

Whether calf DVT requires anticoagulant therapy is currently one of the most debated issues in the field of venous thromboembolism. Although calf DVT is a very common medical condition, only few randomized controlled trials have addressed its treatment to date. Moreover, results of these trials are discordant, half of them suggesting that therapeutic anticoagulation should be prescribed, while some of them do not report a clear benefit of therapeutic anticoagulation. Three of these trials were open-label and had many methodological limitations, while the only placebo-controlled trial was hampered by a limited statistical power.

Nevertheless, existing evidence suggests that not all calf DVT deserve therapeutic anticoagulation. As shown in the randomized placebo-controlled trial, the benefit-risk ratio of anticoagulation is highly debatable in low risk patients, as treatment is associated with a non-statistically significant decrease of symptomatic thromboembolic events, but at the expense of a statistically significant increase in the rate of major or non-major clinically relevant bleedings. Therefore, it is quite possible that low risk patients (e.g. patients without active cancer, outpatients, and patients without previous VTE) are better served without therapeutic anticoagulation and should undergo ultrasound surveillance.

This latter point supports the current ACCP guidelines, which suggest that low-risk patients with symptomatic calf DVT, such as patients without a previous DVT or active malignancy, could safely be managed with serial ultrasound testing and no anticoagulant therapy [4,62].

Moreover, not treating with anticoagulants all calf DVT could be an important cost-saving strategy, as calf DVT represents half of diagnosed DVT [9].

Recent approval of the direct oral anticoagulants (DOACs) could also impact future strategies. Until recently, the use of anticoagulants in patients with calf DVT was limited by the cost and especially the invasive nature of daily LMWH injections, or the cumbersome initiation and management of warfarin therapy. The risk-benefit balance of DOACs has not been evaluated for this indication as of yet, and large prospective trials are needed. The use of a prophylactic dose of anticoagulants could also represent another alternative in the future as it could potentially reduce the symptomatic VTE rate and decrease the bleeding rate when compared to therapeutic treatment. In patients with superficial vein thrombosis, a prophylactic dose was shown to be associated with a reduction in the rate of thromboembolic complications, without any increase in the risk of bleeding [66]. However, no formal validation of this attitude is nowadays available for thrombosis involving the deep venous system. Whether a prophylactic dose of anticoagulants could be an alternative for distal DVT remains to be determined.

In conclusion, low risk patients with symptomatic distal DVT may benefit more from elastic compression stockings and ultrasound monitoring rather than therapeutic anticoagulant treatment. At the moment and despite the lack of clear data, it seems wise to still give therapeutic anticoagulation to patients with active cancer, to patients with previous VTE, to patients with unprovoked distal DVT, and maybe to inpatients not at high bleeding risk, but this may be challenged by future studies.

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