The lower leg vein thrombosis – a disease for specialists

J. Herold; R. Bauersachs

Klinik für Gefäßmedizin – Angiologie, Gefäßzentrum, Klinikum Darmstadt GmbH, Darmstadt

Keywords

Isolated calf vein thrombosis, isolated calf muscle vein thrombosis, thromboembolism, deep vein thrombosis.

Summary

For patients with proximal deep vein thrombosis or pulmonary embolism, the initial treatment is well defined. However, there are conflicting recommendations from current guidelines when distal (calf) veins are thrombosed, ranging from surveillance without anticoagulation to full therapeutic anticoagulation for three months or even longer, as the dose and duration of the anticoagulant is not yet established due to sparse and contradicting evidence. This article is intended to critically review the available evidence and facilitate patient-specific treatment recommendations based on current studies, guidelines and expert opinion.

Schlüsselwörter

Muskelvenenthrombose, isolierte Unterschenkelthrombose, Thromboembolie, distale Thrombose.

Zusammenfassung

Für Patienten mit proximalen Thrombosen oder Lungenembolien ist die antikoagulatorische Behandlung klar definiert. Sind distale Venen thrombosiert gibt es in den aktuellen nationalen und internationalen Leitlinien widersprüchliche Empfehlungen, welche von therapeutischer Antikoagulation über 3 Monate oder länger, über intermediäre Antikoagulation über einen kürzeren Zeitraum bis hin zum Verzicht auf Antikoagulation bei klinischer Überwachung reichen. Dieser Artikel soll hierüber anhand der Zusammenstellung aktueller Studien, Leitlinien und Expertenmeinungen die doch meist patientenindividuelle Therapieempfehlung kritisch beleuchten und dann erleichtern.

Correspondence to:
Prof. Dr. med. Rupert Bauersachs
Grafenstraße 9
64283 Darmstadt
Tel. 06151 – 107 4401
Fax 06151 – 107 4429
E-Mail:
Rupert.Bauersachs@mail.Klinikum-Darmstadt.de

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Introduction

Distal vein thrombosis, more precisely "isolated" distal thrombosis, is a (deep) vein thrombosis of the paired calf veins or muscle veins, or a combination of both. Synonyms used include "calf vein thrombosis" or "one-level thrombosis", or in English-speaking countries, "isolated deep distal vein thrombosis" (IDDVT) or "isolated calf vein thrombosis" (ICVT). If the thrombosis extends to the trifurcation – the site where the fibular and tibial veins flow into the popliteal vein – it is called a proximal deep vein thrombosis (pDVT) (1). In contrast to proximal thrombosis, the treatment regimen for muscle vein thrombosis (MVT) or ICVT is not clearly defined (2, 3). The aim of this article is to critically examine and facilitate treatment recommendations on the basis of current studies, guidelines and expert opinions.

Studies on distal thrombosis and muscle vein thrombosis

The TULIPA registry (4) analysed the risk profile of community-acquired DVT and the diagnostic and therapeutic management in Germany. Almost 400 practices, in which a total of 4,956 patients with suspected thrombosis were investigated, took part in this registry. The registry results showed that the isolated distal veins were affected in roughly half of the diagnosed thromboses. MVT, alone or in addition, accounted for almost 50% of the distal thromboses (dDVT). In other investigations, such as the OPTIMEV study (5), the distribution pattern was somewhat different with about 50% MVT, 25% axial dDVT and approx. 25% combinations.

The diagnostic reliability of complete compression ultrasonography (CCUS), i.e. including the calf, appears adequate to start or reject anticoagulation treatment (1). It is known from the research group of Schellong et al. that with negative CCUS, only 0.57% (0.25–0.89%) of patients develop venous thromboembolism (VTE) after three months if oral anticoagulation (OAC) is not initiated (6). The rate of recurrence under routine German conditions, i.e. the "failure rate" in the case of clearly negative CCUS, was 0.34% (0.09 – 0.88%) (6, 7). However, this low rate could only be achieved with good investigation conditions and objectively clear results (6, 8). If the initial CCUS was not clear or the investigator was uncertain whether or not a thrombosis was present, there were significantly more VTE after three months, namely 2.5% (0.69 – 6.28%).

Important conclusions about the management of distal thrombosis can be drawn from a recent review on dDVT by Robert-Ebadi et al. (9): on the basis of more than

10,000 patients with suspected DVT, the diagnosis was confirmed in 23% of patients. 49% of the patients who were actually affected showed a pDVT and 51% a dDVT. If no anticoagulation was carried out with initially negative CCUS, then the 3-month rate of DVT was 0.6%, which corresponds to the results of the study of Schellong et al. (10). Robert-Ebadi et al. showed that a DVT was only documented in two patients (0.9%, 95% CI: 0.1–3.3%) of those with negative CCUS who underwent a clinical follow-up after 168 ± 25 days, (9). This study also investigated whether there was a difference in the sensitivity of the laboratory workup between the proximal and distal thromboses. The study showed that the sensitivity of the ELISA D-dimer test for pDVT was higher than for dDVT (98% vs. 86%) (9). This difference was also confirmed with 94% vs. 79% for the latex agglutination test and with 84% vs. 64% for the test with whole blood agglutination (9). It is assumed that this difference is due to the larger amount of thrombus and hence increased fibrin cleavage products with sites in the thigh.

However, it must be recognised that the specificity of the D-dimer measurement is too low to prove a thrombosis solely from a concentration increase in the blood. The only worthwhile use of the D-dimer test is after prior estimation of the clinical probability (CP), e.g. based on the criteria defined in the Wells score. A negative D-dimer value with low CP means that no treatment-requiring thrombosis is present and the patient does not require any further diagnostic workup in this regard (2). On the other hand, with high CP, D-dimer tests should not be used in general because their negative predictive value in this situation is not sufficiently high and in the case of a negative test result, further workup might be incorrectly omitted (2, 11–13).

How often does dDVT cause a pulmonary embolism?

This question was evaluated in a recent systematic review (14) of eight randomised studies and 13 prospective cohort studies. It was shown that the incidence of a pulmonary embolism (PE) on the basis of an isolated dDVT was between 0% and 6.2%. No fatal PE was observed in this study (14). If existing PEs on first presentation were also taken into account, then the rate was 5.1% – 43.4% (median 12.8%); on the other hand a PE rate of 0–6.2% (median 1.1%) was found in 16 studies that had explicitly excluded an initial, concurrent PE. Since neither PE in asymptomatic patients nor fatal PE were recorded, the PE rates here are underestimated. Overall, these studies showed that a PE after dDVT was rare and the clinical severity often remained unclear.

However, the data were very heterogeneous with respect to patient characteristics, diagnostic methods and follow-up. For example, PE was diagnosed using a ventilation/perfusion scan, whereas current studies predominantly use CT angiography. Another aspect for consideration when interpreting such study results is the fact that on demonstration of PE and isolated dDVT, the PE could have arisen from a pre-existing pDVT and only a dDVT was still present in the subsequent ultrasound scan. Vice versa, it emerged that not every patient with dDVT in the studies underwent CT investigation for additional PE. Another fact that should be emphasised is that 80% of patients with PE suffered a recurrence in the pulmonary circulation and only in 20% was a circulatory area other than the isolated peripheral thrombosis affected as a recurrence (15, 16). The study of Douketis et al. also confirmed the opposite – 80% of peripheral thromboses led to a recurrent thrombosis without PE (17).

Current guidelines: recommendation concerning the treatment of distal thromboses

With a very weak grade of recommendation (2C) for dDVT without serious symptoms or with a high risk of bleeding and without risk factors for thrombus ascension, the current American guidelines of the American College of Chest Physicians ACCP (3) propose that instead of anticoagulation, the ultrasound should merely be repeated (Grade 2C, i.e. weak evidence). Anticoagulation is recommended only in the case of severe symptoms or existing risk factors (1B) (▶ Table 1).

The following parameters are listed as risk factors for thrombus extension: positive D-dimer result, extensive thrombosis (> 5 cm long, > 7 mm diameter) or close to a proximal vein. If persistent trigger risk factors such as active cancer, previous VTE or in-patient status are present, then anticoagulation is proposed for at least three months (1B). In contrast to thrombosis of the axial deep veins, a lower risk of progression is assumed for MVT and therefore merely a repeat duplex investigation after 2 weeks (2C). If the ultrasound check reveals thrombus extension into the calf veins, then anticoagulation is also proposed (2C), in the case of proximal extension, anticoagulation is recommended (1B). If the constellation leads to initiation of anticoagulation, the dose and duration of treatment corresponds to that of acute pDVT(1C).

According to the recommendations of the interdisciplinary German S2k Guidelines of the German Society for Angiology a patient with dDVT should be anticoagulated for no longer than three months.

These recommendations are also given for a recurrence or an idiopathic distal thrombosis (2). Distinctions between MVT and dDVT are not made, and in the sense of an individualised decision, a shorter duration of treatment and/or a reduced dose of the anticoagulant is possible.

The guidelines of the European Society of Cardiology (ESC) (18) updated in 2017, recommend three months of anticoagulation in patients with a high risk of recurrence and anticoagulation for 4–6 weeks with a low risk either at a therapeutic or reduced dose (▶ Table 1). Alternatively to drug therapy, ultrasound monitoring without anticoagulation is also offered.

Risk factors for the occurrence of dDVT

In the prospective, multicentre observational study OPTIMEV (Optimizing history taking for evaluating the risk of venous thromboembolism) (5, 19), patients

Tab. 1 Current guidelines for the treatment of distal thrombosis; *High risk (modified from [18]): Persistent risk factor (RF), unprovoked, persistently impaired mobility, hospitalisation, male sex, previous VTE, age >50 years, extension into the trifurcation, >1 calf vein affected, dDVT in both legs; **Low risk: Transient RF, Post-OP, plaster, trauma, long-distance journey, immobilisation, contraceptive pill or hormone replacement therapy (if discontinued)

Association	German Society for Angiology (DGA) S2k-LL (2)	European Society of Cardiology (ESC) (18)	American College of Chest Physician (ACCP) (3)
Duration of anticoagulation	≤ 3 months also if recurrence or idiopathic	3 months if risk of recurrence is high*	MVT rated as lower risk (2C) Therapeutic anticoagulation: only if severe symptoms or risk factors (1B)
Adjustment	Individually also shorter, also lower dose possible	With low risk**: 4–6 weeks of treatment	No anticoagulation with low risk or no symptoms, but ultrasound after 2 weeks (2C)
Special features	If risk factors such as cancer or antiphospholipid syndrome are present, then longer anticoagulation No difference between MVT/dDVT	With low risk lower dose possible or monitoring (ultrasound)	With risk factors ≥ 3 months (1B) • pos. D-dimers • > 5 cm length • > 7 mm diameter • Close to prox. veins • Cancer • Previous VTE • Inpatient status • High risk of bleeding (2B)

with objectively confirmed symptomatic dDVT were enrolled and compared with those presenting with pDVT. Of the 6,141 patients with suspected thrombosis, an isolated distal thrombosis was significantly more frequent than a pDVT (56.8% vs. 43.2%; p = 0.01). dDVT was more often associated with transient risk factors such as recent surgery or plaster immobilisation; recent travel was also counted as a risk factor (5, 19).

On the other hand, pDVT was significantly more often associated with chronic diseases such as cancer, heart failure or respiratory insufficiency or with age > 75 years (▶ Table 2). The majority of patients (96,8%) with DVT received anticoagulation therapy. Despite the fact that there was no difference in the occurrence of recurrences and major bleeds, the mortality rate of patients with pDVT was significantly higher than in patients with isolated dDVT (8.0 vs. 4.4%; p <0.01) (19).

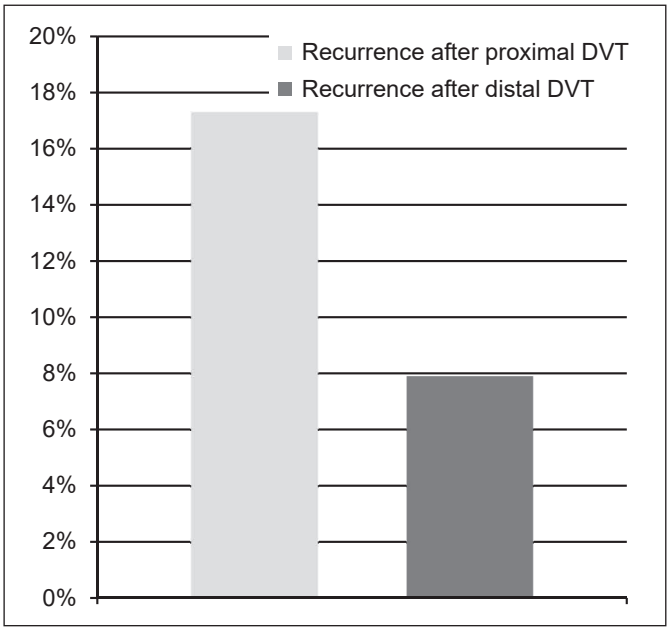

Fig. 1 Risk of VTE recurrence. The median follow-up (of survivors) was 94 months after pDVT and 84 months after dDVT. Over 3,175 patient years, 15.0% recurrent symptomatic pDVT or PE were observed, of which 17.3% occurred after pDVT (right) and 7.9% after dDVT (left), corresponding to event rates of 4.5%/year (3.7–5.4) for pDVT and 2.0%/year (1.1–3.3%) for dDVT. Overall, dDVT was associated with a lower risk of recurrence [HR 0.49 (0.32–0.74)].

Risk factors for the occurrence of recurrent VTE after dDVT

In the previously mentioned OPTIMEV study (5), the incidence of VTE recurrences in patients without cancer after the first dDVT were compared with the incidence of initial pDVT three years after the index VTE and the end of anticoagulation. This analysis showed that the annualised VTE recurrence rate was lower with dDVT than with pDVT. Interestingly, however, the rates of pulmonary embolism were comparable in the two groups: 1.0% (0.5–2.3%) vs. 0.9% (0.5–1.6%); p = 0.83). In addition, a recurrent dDVT occurred more frequently in patients who had suffered a primary dDVT and in reverse a recurrent pDVT was more common in patients with initial pDVT (▶ Table 3) (5).

It can be seen from ▶ Table 3 that a) age over 50 years, b) an unprovoked dDVT, c) thrombosis in more than one vein in one leg or d) thromboses in both legs, trebles the risk of recurrence. For all factors, the risk of recurrence is more than 3% per patient year. Interestingly, neither sex nor the presence of an MVT, nor the involvement of deep calf veins, the thrombus diameter or the duration of anticoagulation for more than 90 days, affects the risk of recurrence.

Tab. 2 Risk factors and their assessment for the occurrence of a proximal or distal thrombosis and their inter-correlation. Patients in whom the corresponding criterion was absent were chosen as controls. Results from the OPTIMEV study (19).

Risk factors	Proximal DVT vs. control patients OR [CI 95%]	Distal DVT vs. control OR [CI 95%]	Distal DVT vs. proximal DVT OR [CI 95%]
Recent plaster (yes vs. no)	2.6 [1.5–4.4]	5.4 [3.9–7.7]	2.2 [1.3–3.8]
Recent surgery (yes vs. no)	1.3 [1.0–1.8]	2.3 [1.9–2.9]	1.8 [1.3–2.5]
Recent long-distance travel (yes vs. no)	2.1 [1.2–3.6]	4.1 [2.8–6.2]	1.7 [1.0–2.8]
Varicose veins (yes vs. no)	0.7 [0.5 – 0.9]	0.9 [0.8 – 1.1]	1.3 [1.0 – 1.7]
Heart/respiratory insufficiency (yes vs. no)	3.0 [2.1 –4.4]	1.5 [1.0–2.2]	0.6 [0.4–0.9]
Age > 75 vs. <50	2.0 [1.5–2.6]	1.1 [0.9–1.4]	0.5 [0.4–0.7]
Active cancer (yes vs. no)	3.2 [2.5–4.1]	1.5 [1.2–1.9]	0.5 [0.4–0.7]

Tab. 3 Risk factors after ending anticoagulation for recurrent thrombosis with initial distal thrombosis compared with patients in whom the criterion was absent. Data from the prospective, multicentre observational study OPTIMEV (5).

Risk factor	Multivariate HR	Recurrent-VTE (%/patient years)
Bilateral DVT	4.0 (1.4–11.1)	8.9 (3.7–21.4)
Multiple unilateral DVT	2.9 (1.4–6.1)	4.9 (3.1–7.8)
Unprovoked DVT	3.1 (1.4–6.9)	3.8 (2.6–5.6)
Age > 50 years	3.7 (1.0–10.6)	3.8 (2.6–5.5)

Recurrent VTE and survival of patients with dDVT compared with patients with pDVT

A retrospective analysis evaluated consecutive patients from 2000–2012 with acute distal and pDVT but no accompanying PE (20). This study showed that dDVT has a lower risk of recurrence than pDVT. 831 patients from 4,759 datasets were included in this analysis. Of these patients, 629 had a symptomatic pDVT, 202 a dDVT, of whom 49.6% had an MVT and 27.1% a thrombosis of the deep calf veins. In 13.4% both an MVT as well as a thrombosis of the deep veins or dDVT of both legs was diagnosed. The patients received anticoagulation therapy for a duration and at a a dose corresponding to the guideline recommendations valid at the time (20).

After a follow-up of eight years, recurrent symptomatic pDVT or PE were observed in 15.0% of patients, of which 17.3% were after pDVT and 7.9% after dDVT, corresponding to event rates of 4.5%/year for pDVT and 2.0%/year for dDVT.

Overall, dDVT was associated with a lower risk of recurrence. The all-cause mortality was 31.6%, corresponding to 4.8%/year. Of the 263 patients who died, 52 had dDVT, corresponding to 25.7% of all dDVT patients and 211 pDVT (33.5% of the total number of pDVT) (▶ Fig. 2). This cohort study showed that patients with a first-event dDVT show a significantly lower risk of recurrent VTE than those with initial pDVT. Women were over-represented in the group with dDVT (56.4% vs. 48.6% with pDVT) and likewise some of the trigger factors (such as surgery or trauma) (20).

Cancer-associated dDVT

Although isolated dDVT is often associated with a malignancy, the long-term course after cancer-associated dDVT had not been investigated to date. In the prospective multicentre observational study OPTIMEV (21), the incidence, after three years, of death, VTE recurrence and major bleeds with cancer-associated dDVT was compared with cancer-associated pDVT. The two groups were equally distributed through Propensity Score Matching in terms of age and sex. The study thus showed that the 92 patients with dDVT had a risk of death and severe bleeds comparable to the 92 patients with pDVT, although their risk of VTE recurrence was higher (▶ Fig. 4).

Compared with dDVT patients without cancer, the dDVT cancer patients had a 9-fold higher risk of death (3.5%/year vs. 38.3%/year; in addition the risk of major bleeds was also higher (1.8%/year vs. 3.6%/year) and for VTE recurrence (21).

Placebo study in dDVT with low risk (CACTUS)

There are five randomised studies on the treatment of dDVT, some of which are over 30 years old, performed with vitamin K antagonists (VKA) and hence no longer corresponding to the current reality (22–24).

Only the CACTUS study (25) provided important new information on the management of dDVT. This was a randomised, placebo-controlled study undertaken in 23 centres in Canada, France and Switzerland in outpatients with a first-ever dDVT and a low risk of recurrence, i.e. patients without active cancer or a previous VTE. The 259 enrolled patients received either 171 IU/kg nadroparin (122 patients) or placebo (130 patients) for a period of six weeks. In addition, they were given compression stockings and were followed up for 90 days. Unfortunately, patient recruitment into the CACTUS study was considerably delayed, so that from February 2008 to November 2014 only 259 patients (half of the planned number) were recruited for the study. Due to the placebo-controlled design with slow recruitment, the study was prematurely discontinued in November 2014.

The primary endpoint comprised extension into proximal veins, a contralateral pDVT or PE after six weeks. There was no significant difference between the two groups in the primary endpoint, which was reached in 3.3% under nadroparin and in 5.4% in the placebo group (p = 0.54) (25). Bleeds occurred in five patients (4%) in the

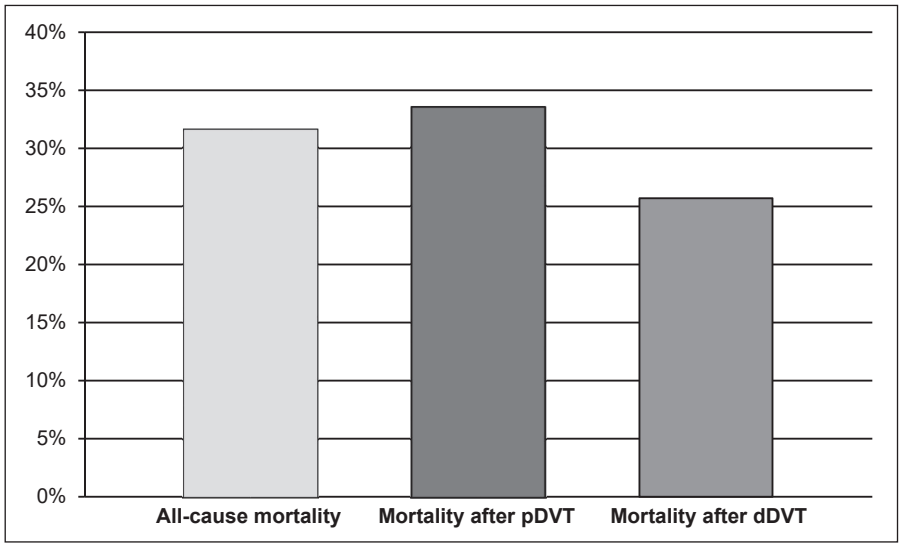

Fig. 2 All-cause mortality was 31.6%, corresponding to 4.8%/year. Of the 263 patients who died, 52 had dDVT, corresponding to 25.7% of all dDVT patients and 211 pDVT (33.5% of the total number of pDVT), corresponding to a HR of 0.75 (0.55–1.02). *The median follow-up (of the survivors) was 94 months after pDVT and 84 months after dDVT. Data from a cohort study (20).

nadroparin group and in none of the patients in the placebo group (corresponding to a risk difference of 4.1: 95% confidence interval 0.4 – 9.2; p = 0.0255). One patient in the nadroparin arm died from metastatic cancer and one patient was diagnosed with HIT II (25). With this study result, administration of nadroparin compared to placebo did not reduce the risk of proximal thrombosis extension nor prevent VTE events in an outpatient low-risk population with dDVT. However, as expected, there was an increased risk of bleeding under nadroparin (25).

How should a distal thrombosis be anticoagulated?

Franco et al. 2017 undertook an interesting meta-analysis to answer the question as to the therapeutic relevance of anticoagulation of a distal vein thrombosis and to derive the duration of anticoagulation (26): The primary endpoint in this evaluation of randomised and cohort studies was a recurrent VTE, including pDVT extension and PE.

Anticoagulation versus no anticoagulation

20 studies with a total of 2,936 patients were evaluated. Five studies were randomised controlled studies and seven were prospective and seven retrospective. However there were differences, for example, in the patient collective: five studies focussed on surgical patients, five on MVT, three each on hospitalised or outpatients. Most studies used ultrasound to diagnose thrombosis, and a few used phlebography or other methods. In five studies, the antithrombotic treatment consisted of a prophylactic and in 14 a therapeutic dose. Treatment duration also varied between two weeks to two years. This fact alone explains the difficulty in transferring the study results to everyday clinical practice.

Nevertheless, the pooled analysis of the 20 studies showed that anticoagulation achieved a significant reduction in recurrent VTE (6.5% vs. 12%) (26). If only the 16 studies with therapeutic anticoagulation were taken into account to answer the question of the need for anticoagulation with dDVT, then the advantage of anticoagulation in preventing VTE recurrence was obvious (6.5% vs. 12.4%). However, there was considerable heterogeneity, especially in the cohort studies. The rate of PE was also lower in the anticoagulated patients than in the control group (1.4% vs. 2.4%) (▶ Fig. 3) (26).

Some of the studies either reported no bleeding complications at all or not in a standardised manner, so that the rate of bleeding could only be evaluated in nine studies (corresponding to 1,385 patients). Although total bleeds under anticoagulation were double as many as under no anticoagulation (6.3% vs. 2.8%), the rate of major bleeds did not differ between the groups (0.4% vs. 0.7%) (▶ Fig. 3).

However, one weakness of this assessment is the low methodological quality and heterogeneous nature of the studies: for example, not all studies evaluated symptomatic events and the anticoagulation treatment used varied markedly. Furthermore, the treatment ranged from vitamin K antagonists (warfarin and phenprocoumon), low molecular weight heparins at a therapeutic or prophylactic dosage to subcutaneous Xa inhibitors. In no study were direct oral anticoagulants (DOACs) used. An equally wide variability was present in the use of compression stockings or the information about the use of aspirin or non-steroidal anti-inflammatory drugs (NSAID).

For how long should anticoagulants be given: 6 weeks or 6 months?

Four studies (27–30) with a total of 1,136 patients compared short anticoagulation (six weeks) with a long period: three studies for 3 months (27, 29) and one study for 6 months (30). The pooled analysis of the studies (26) showed a reduction in recurrent thromboses under extended anticoagulation compared to studies without anticoagulation (OR 0.50, 95% CI 0.31–0.79), with no significant increase in the risk of major bleeds (OR 0.64, 95% CI 0.15–2.73). PE was also far less common under anticoagulation (OR 0.48, 95% CI 0.25–0.91). Bearing in mind the various definitions of bleeds, there were indeed higher overall bleeding rates with long periods of anticoagulation, but major bleeding events were not significantly increased.

Discussion

The data from which a treatment, dose and duration of anticoagulation in patients with dDVT are derived are inconsistent and recommendations vary between surveillance without any anticoagulation to anticoagulation at a therapeutic dose, sometimes for even longer than 3 months.

In contrast, there is a clear regimen of a therapeutic dose for at least 3–6 months for proximal thromboses (2, 18, 27, 31). The wealth of recently published data on dDVT now gives, for the first time, a clear classification of this common, but in large-scale studies hitherto underrepresented disease. In particular, the data now permit a more reliable risk stratification and a better benefit-risk assessment of anticoagulation in the presence of dDVT. Distal thromboses have an even more important significance in patients with an underlying malignant disease and it is therefore essential that they are correctly diagnosed and treated (21, 32, 33).

In our view, the previously discussed meta-analysis of Franco et al. (26) is of great importance because it analysed the data sets of 20 studies with over 4,000 patients. It showed that in dDVT, anticoagulation – at both a prophylactic and a therapeutic dose – reduced the rate of recurrence of thrombosis and decreased the risk of PE by 50%. The bleeding rate under anticoagulation was admittedly increased, but there were no significant differences in relation to major bleeds. Thus the authors compared the 1.4% risk of PE without anticoagulation against the 0.4% risk of a severe bleed. The conclusion of the authors, that, due to the improved benefit-risk ratio, practicability and oral administration, DOACs should be considered, is however not yet supported by the data for dDVT.

The CACTUS study (14) was ended prematurely due to lack of funding, expiry of study medication and slow recruitment after less than half the planned patients had been enrolled. In view of the placebo arm, patients at higher risk were excluded; this fact leads to the supposition that study investigators may not have enrolled patients with a suspected elevated risk. With limited statistical validity, it is questionable whether the results show that low-risk patients with dDVT actually require anticoagulation. This group of patients and those with a high risk of bleeding should not be anticoagulated, but be monitored by ultrasound after one to two weeks or on symptom progression. This strategy is however, generally not practicable in an outpatient setting. So for these patients, in future low doses of LMWH, fondaparinux or DOAC for about 40 days could be offered, corresponding to the regimen for superficial vein thrombosis in the CALISTO (34) or SURPRISE study (35).

The OPTIMEV study, in contrast, demonstrated that cancer patients with dDVT have a high risk of VTE recurrence (21), cancer patients with dDVT have a similarly poor prognosis to those with pDVT and a considerably worse outcome than dDVT without a malignant disease. This underlines the clinical significance of cancer-associated dDVT.

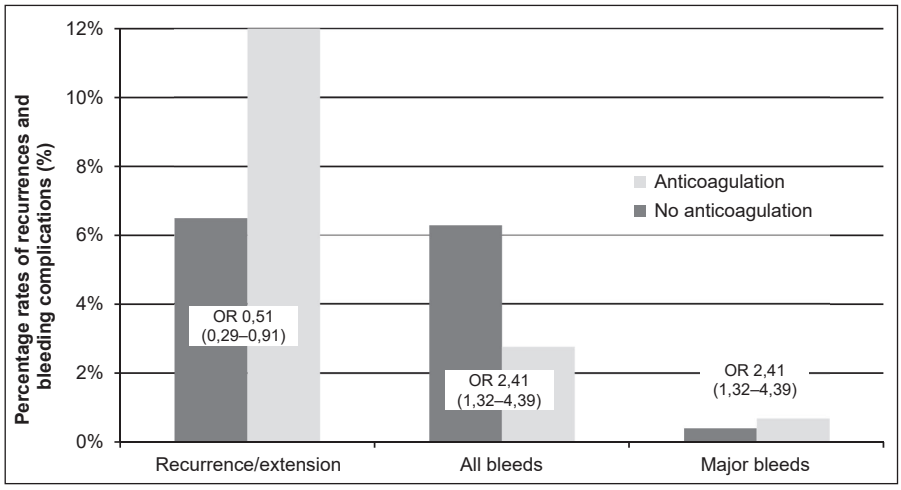

Fig. 3 VTE recurrence and thrombosis extension, as well as bleeding complications after dDVT under prophylactic or therapeutic anticoagulation compared to no anticoagulation. Data from a meta-analysis (26).

Conclusions for practice

Whereas a clear regimen of a therapeutic dose for at least 3–6 months exists for proximal thrombosis (2, 18, 27, 31), the treatment recommendations for dDVT vary from pure monitoring without anticoagulation to anticoagulation at a therapeutic dosage for even longer than 3 months.

The differing recommendations and uncertainties in the management of the disease are due to a considerably larger heterogeneity of dDVT in comparison with pDVT in many respects:

1. From a pathophysiological perspective, the course of dDVT is more heterogeneous and may also be self-limited, so that transient or persistent RFs have a greater effect on progression. On the other hand, in the case of proximal thromboses, through the extension into the popliteal vein, a clear predominance of prothrombotic factors is documented.
2. Diagnostically, due to the necessity to investigate a considerably greater number of veins (posterior tibial, fibular and anterior tibial, as well as up to 20 muscle veins), dDVT is far more challenging than proximal thrombosis.
3. In terms of differential diagnosis, the lower specificity of CCUS in dDVT [94 – 98% (19)], means that 2 – 6% of false-positive results are recorded, leading to unnecessary anticoagulation.
4. Acute complications of anticoagulation are increased on confusion with other diseases such as muscle fibre rupture, Baker's cysts or muscle trauma.
5. The risk/benefit ratio of anticoagulation, and hence patient selection, varies considerably and is often more difficult to determine than with pDVT.
6. The mortality rate of dDVT varies over a considerably wider range than with pDVT and is therefore more difficult to estimate.

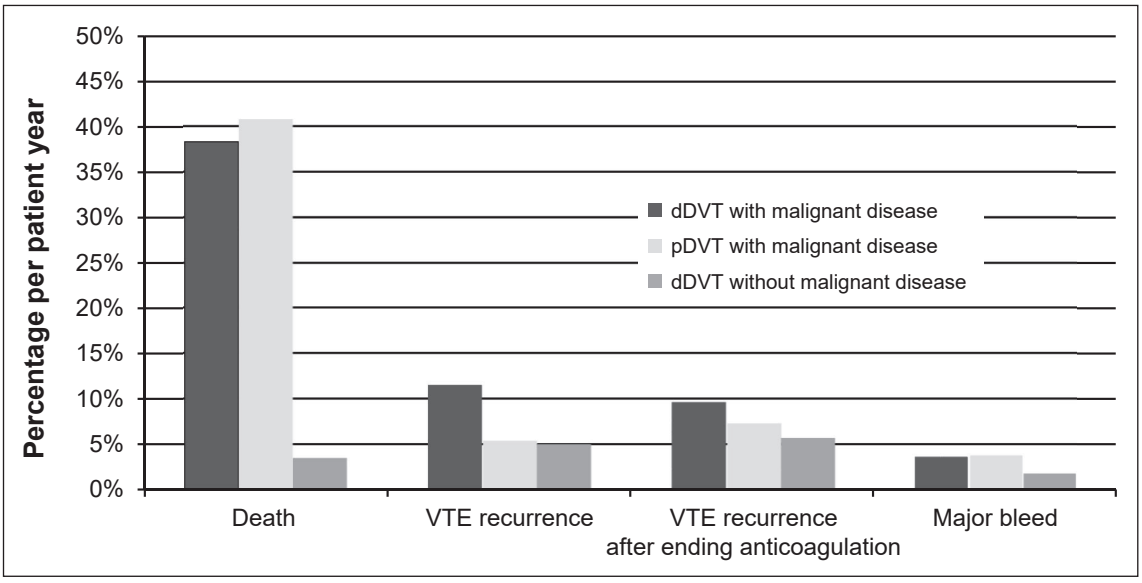

Fig. 4
Outcome after distal and pDVT in patients with underlying malignant disease: from left to right, mortality, VTE recurrence, VTE recurrence after ending anticoagulation and the occurrence of major bleeds in dDVT patients with and without cancer compared and contrasted with the outcome of pDVT. Data from the prospective, multicentre OPTIMEV observational study (21).

7. The risk of recurrence of dDVT is very heterogeneous, and hence also the need for and duration of anticoagulation; this ranges from very low risk with clear triggers up to a very high risk, e.g. with malignant diseases.
8. It is therefore far more important and difficult to assess the risk factors in dDVT than in pDVT.

Compared with pDVT, dDVT is the more complex, error-prone disease and its management is undoubtedly more challenging. This management therefore belongs in the hands of specialists, so as to avoid false assessments and wrong decisions.

Thus dDVT places high demands on the treating clinician.

Consequences for practical management

- The standard diagnostic method for dDVT in Germany is complete compression ultrasonography (CCUS).
- If the risk of recurrence is low (▶ Table 1), CCUS can be repeated, without anticoagulation, after two weeks or on symptom progression and this suffices as management; in addition thrombosis prophylaxis can be started if a transient risk factor (e.g. impaired mobility) is documented.
- Alternatively, anticoagulation can be given for a limited period (even shorter than 3 months); the guidelines also permit lower rather than full therapeutic doses.
- A careful clarification of differential diagnoses, such as muscle fibre rupture, Baker's cysts or intra-muscular bleeding must be undertaken before beginning anticoagulation.
- If the risk of bleeding is high, or the results are uncertain, CCUS should be repeated after one week. Here too, the use of temporary thrombosis prophylaxis can be worthwhile after individual consideration of additional transient risk factors.
- If the risk of thrombosis recurrence is high (▶ Table 1) a full therapeutic dose for 3 months, corresponding to the treatment of pDVT is recommended. A patient with dDVT should not be anticoagulated for longer than 3 months. This recommendation is also given for a recurrence or unprovoked distal thrombosis (2, 31, 36).
- Patients with antiphospholipid syndrome, active cancer or ongoing risk factors should be anticoagulated for longer than three months.
- It has not yet been investigated whether the use of low-dose DOACs is equally effective or superior to usual anticoagulation with LMWH or fondaparinux.

Conflict of interests

The authors state that there is no conflict of interests.

Ethical guidelines

Preparation of the manuscript did not involve any studies on humans or animals.

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