

Venous Thrombosis: Risk Factors and Management

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Abstract

During the past 2 decades, the diagnostic and therapeutic approach to deep vein thrombosis (DVT) has greatly evolved. First, the assessment of the clinical probability has gained wide acceptance. Second, novel noninvasive diagnostic tools such as venous compression ultrasonography and D-dimer measurement have become available, drastically reducing the need for invasive tools such as phlebography. Third, new anticoagulant drugs, in particular low-molecular-weight heparins (LMWHs), have become available and have made DVT treatment a lot easier by allowing out-of-hospital management.

Several diagnostic algorithms, based on the assessment of clinical probability, D-dimer measurement

and venous compression ultrasonography, have shown to be safe in management studies. In addition to improvements in diagnostic algorithms and anticoagulant treatment, compression therapy by elastic stockings to diminish the prevalence of the postthrombotic syndrome has been validated in prospective studies.

The dilemma of the need or no need for looking for and treating isolated calf DVT with anticoagulants remains a controversial issue, as do the optimal length and intensity of anticoagulation. In the near future, the emergence of several new, totally synthetic, orally active anticoagulant compounds, such as direct thrombin or factor Xa inhibitors that are presently being tested in clinical studies, could profoundly change the therapeutic approach to DVT.

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Key Words:

Deep vein thrombosis · Clinical probability · D-dimer · Lower-limb compression ultrasonography · Anticoagulation

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Tiefe Venenthrombose: Risikofaktoren und Management

Zusammenfassung

In den letzten 2 Jahrzehnten haben Diagnostik und Therapie der tiefen Venenthrombose (TVT) entscheidende Veränderungen erfahren. Erstens hat die Beurteilung der klinischen Wahrscheinlichkeit eine breite Akzeptanz gefunden. Zweitens haben sich nichtinvasive Abklärungsmethoden wie Kompressionsechographie und Bestimmung der D-Dimere durchgesetzt, was die Notwendigkeit einer invasiven Abklärung mittels Phlebographie drastisch reduziert hat. Drittens finden neue Formen der Antikoagulation, im Speziellen die niedermolekularen Heparine, breite Anwendung und erleichtern die Behandlung einer TVT, die zurzeit meist ambulant durchgeführt werden kann.

Zahlreiche diagnostische Algorithmen basieren auf klinischer Wahrscheinlichkeit, Bestimmung der

D-Dimere und Kompressionsechographie und haben sich in Studien als sicher erwiesen. Neben dem Fortschritt der diagnostischen Algorithmen und der Antikoagulation konnten prospektive Studien die Wichtigkeit der Kompressionstherapie mittels elastischer Binden zeigen und eine Verminderung der Prävalenz des postthrombotischen Syndroms bestätigen.

Die Diskussion über die Notwendigkeit einer Abklärung und Behandlung der TVT des Unterschenkels bleibt kontrovers, ebenso die optimale Dauer und Intensität der Antikoagulation. In absehbarer Zukunft könnten einige neue, völlig synthetische, oral aktive Antikoagulanzen, wie direkte Antithrombine oder Anti-Faktor Xa, welche kürzlich in klinischen Studien getestet wurden, die therapeutischen Ansätze bei der TVT grundsätzlich verändern.

Schlüsselwörter:

Tiefe Venenthrombose (TVT) · Klinische Wahrscheinlichkeit · D-Dimere · Kompressionsechographie · Antikoagulation

Introduction

Venous thromboembolism (VTE) and its manifestations, including deep vein thrombosis (DVT) and pulmonary embolism (PE), pose a life-threatening health problem for thousands of people each year. Overall, incidence of deep vein thrombosis is 1–2/1,000 persons/year. However, incidence rises exponentially from less than 5 cases/100,000 persons < 15 years of age to 500–1,000 cases/100,000 persons aged 80 years [1]. Approximately one third of pa-

tients with VTE manifest PE, whereas two thirds manifest DVT alone. Symptoms of DVT include swelling of the affected limb, tenderness, erythema, and pain, whereas PE presents as sudden breathlessness with or without chest pain, or, less frequently, collapse with hemodynamic shock.

During the past 2 decades, the diagnostic and therapeutic approach to DVT has changed in several major ways. First, novel noninvasive diagnostic tools such as venous compression ultrasonography (CUS)

and D-dimer (DD) measurement have become available, drastically reducing the need for invasive tools such as phlebography [2]. Second, new anticoagulant treatment, in particular low-molecular-weight heparins (LMWHs), have become available and have rendered the treatment of DVT easier by allowing out-of-hospital treatment. Third, the index of clinical suspicion has progressively become lower, resulting in the fact that the vast majority (80% or even more) of patients with suspected VTE do not have the disease. Fourth, noninvasive strategies have been validated in large-scale outcome studies, and more attention has been paid to their cost implications [3].

Risk Factors for Venous Thromboembolism

To improve survival, avoid recurrences, prevent complications and reduce health-care costs, the occurrence of VTE must be reduced. To reduce VTE incidence, persons at risk for VTE must first be identified [4], in order to target prevention. Risk factors for VTE include increasing age, surgery, trauma, hospital or nursing-home confinement, active neoplasia with or without concurrent chemotherapy, central vein catheterization or transvenous pacemaker, prior superficial vein thrombosis, varicose veins, and neurologic disease with extremity paresis; patients with chronic liver disease have a reduced risk [5]. Hospitalization and nursing-home residence together account for almost 60% of incident VTE events in the community. Thus, hospital confinement provides an important opportunity to significantly reduce VTE incidence [6]. Of note, hospitalization for medical illness and hospitalization for general surgery account for almost equal proportions of VTE, emphasizing the need to provide prophylaxis to both of these risk groups. A recent epidemiologic study suggested that active cancer may account for almost 20% of incident VTE events occurring in the community [4]. The risk appeared to be higher for patients with pancreatic cancer, lymphoma, malignant brain tumors, cancer of the liver, leukemia, and colorectal and other digestive cancers. Cancer patients receiving immunosuppressive or cytotoxic chemotherapy are even at higher risk for VTE [7]. Central venous catheter or transvenous pacemaker are well known risk factors for upper-limb DVT. However, systematic prophylaxis in these situations is not widely accepted [8, 9].

Among women, additional risk factors for VTE include oral contraceptive use and hormone therapy, pregnancy and the postpartum period, and therapy with selective estrogen receptor modulators, such as raloxifene. First- and third-generation oral contraceptives convey higher risk than second-generation oral contraceptives. Other conditions associated with VTE include heparin-induced thrombocytopenia, myeloproliferative disorders, nephrotic syndrome,

paroxysmal nocturnal hemoglobinuria, thromboangiitis obliterans (Buerger's disease), thrombotic thrombocytopenic purpura, Behçet's syndrome, systemic lupus erythematosus, inflammatory bowel disease, homocystinuria, and possibly, hyperhomocysteinemia. Recently, acute infections of the urinary or respiratory tract in the community setting have also been related with a transient and modest increase in the risk of VTE [10].

Thrombophilias are inherited or acquired abnormalities associated with an increased risk of venous thromboembolic disease. Before 1993, a heritable cause of thrombophilia was detectable in a relatively small proportion of patients presenting with DVT or PE. Such abnormalities were confined to rare deficiencies like antithrombin, protein C or protein S. The recent discovery of other two other prothrombotic mutations (the factor V Arg506Gln, or factor V Leiden mutation and the prothrombin G20210A mutation), quite prevalent (about 5% up to 30% in some part of Sweden) in Caucasians, has highlighted a genetic-mediated basis of VTE [11, 12].

Diagnosis of Deep Vein Thrombosis Clinical Probability Assessment

Sensitivity and specificity of clinical symptoms and signs in suspected DVT are low when considered singly. Nevertheless, clinicians can combine these findings effectively along with elements of personal and family history either implicitly (empirically) or by prediction rules or scores in order to classify patients according to their probability of having the disease, the so-called prior clinical probability [13].

In the setting of suspected DVT, the Wells' score [14] has gained relatively wide acceptance in spite of its partial subjectivity (Table 1). It is probably not more accurate than the simple implicit evaluation [13]. However, it is easier to teach to junior physicians and allows discussing occasional disagreements among experienced clinicians on explicit grounds. Nevertheless, both the implicit assessment and the explicit Wells' score allow usefully categorizing patients in low, intermediate, or high clinical probability groups in which the prevalence of DVT is approximately 5%, 20%, and 80%, respectively [15]. Most patients with suspected DVT have a low or intermediate clinical probability of having the disease. These patients can usually be investigated by entirely noninvasive algorithms, which is an important advantage resulting from the evaluation of clinical probability.

DD Measurement

DD is a degradation product of cross-linked fibrin and its level increases in plasma of patients with acute

VTE. DD, when assayed by a quantitative enzyme-linked immunosorbent assay (ELISA) or by some automated turbidimetric assays, has been shown highly sensitive (> 98%) in acute DVT, usually at a cutoff value of 500 µg/l [16]. Hence, a DD level below this value reasonably rules out acute DVT, at least in patients with a low or intermediate prior clinical probability [16]. Table 2 summarizes the pooled analysis of the published literature on most commercially available rapid DD tests. Tests vary with respect to several characteristics, including assay technique (ELISA, latex, or automated turbidimetric tests), specificity of monoclonal antibodies used, calibrators, and quantitative or semiquantitative results.

In summary, highly sensitive DD assays allow exclusion of DVT in outpatients with a low or intermediate clinical probability, while whole-blood agglutination tests only rule out the disease in patients with a low clinical probability [17]. Finally, DD is unlikely to be useful in very elderly patients or in hospitalized patients with suspected VTE [18] because of diminishing specificity of the measurement with increasing age.

Venous CUS

In studies using phlebography as gold standard, lower-limb venous CUS, an entirely noninvasive test, has a sensitivity of 97% (95% confidence interval [CI]: 96–98%) and a specificity of 98% for symptomatic proximal DVT [2]. It has become the cornerstone of DVT diagnosis in clinically suspected individuals [19, 20]. The single well-validated diagnostic criterion for DVT on CUS is absence of full compressibility of the deep vein when applying pressure through the ultrasound probe. Intraluminal venous ultrasonography has been reported to have variable accuracy, and neither changes in venous diameter during Valsalva maneuver nor assessment of Doppler flow have been found to improve diagnostic accuracy for DVT [2].

Proximal Versus Proximal and Distal CUS

The observation of a very low 3-month thromboembolic risk in patients with a negative CUS of the proximal veins and with clinically suspected DVT (around 1% in management studies [13, 21–24]) questions the need for diagnosing so-called calf (or distal, infrapopliteal) DVT, at least in non-high clinical probability patients. Indeed, in such patients, detecting clots in the posterior tibial or peroneal veins or even in calf muscle veins may be double-edged: on the one hand, the potential of reducing the 3-month thromboembolic risk is limited (because it is already quite low), and, on the other hand, the risk of false-positive findings and subsequent unnecessary anticoagulant treatment in patients who could be left untreated, is quite

Items	Points
Cancer	+ 1
Paralysis or recent immobilization	+ 1
Bedridden > 3 days, or surgery/trauma < 4 weeks	+ 1
Pain on palpation of the deep veins	+ 1
Edema of thigh and calf	+ 1
Pitting edema (symptomatic side only)	+ 1
Dilated superficial veins (symptomatic side only)	+ 1
Alternative diagnosis at least as likely as DVT	- 2
Clinical probability	
Low	≤ 0
Intermediate	1-2
High	≥ 3

Table 1. The Wells' score for assessment of prior clinical probability of deep vein thrombosis (DVT).

Tabelle 1. Klinische Wahrscheinlichkeit einer tiefen Venenthrombose (DVT): Wells-Score.

Table 2. Performances of various D-dimer (DD) assays for diagnosing venous thromboembolism (VTE). Results are almost identical for suspected deep vein thrombosis and for suspected pulmonary embolism. CI: confidence interval.

Tabelle 2. D-Dimer-(DD-)Bestimmung für die Diagnose der venösen Thromboembolie (VTE). Die Resultate für den Verdacht auf tiefe Venenthrombose und Lungembolie sind annähernd identisch. CI: Konfidenzintervall.

Test (producer)	n (nVTE)	Sensitivity [% (95% CI)]	Specificity [% (95% CI)]
ELISA tests			
VIDAS DD (bioMérieux) ^a	3,575 (809)	99 (98–100)	44 (42–45)
Instant IA ^b (Stago)	1,549 (686)	92 (89–94)	54 (50–58)
Nycocard ^b (Nycomed)	938 (337)	92 (89–95)	45 (41–49)
Latex^b or automated turbidimetric tests			
SimpliRED ^b (Agen) ^a	2,303 (567)	85 (82–88)	69 (66–71)
Liatest (Stago)	1,113 (370)	95 (92–97)	39 (36–43)
MDA (Organon Technika)	642 (133)	96 (91–99)	46 (41–51)
Minutex ^b (Biopool)	565 (264)	89 (84–93)	58 (52–64)
DDPlus (Dade Behring)	481 (154)	96 (91–99)	46 (40–51)
Tinaquant (Boehringer Mannheim) ^a	286 (162)	99 (96–100)	40 (31–49)
Turbiquant (Dade Behring)	183 (19)	89 (67–99)	57 (49–64)
LPIA D-Dimer (Mitsubishi)	87 (42)	95 (89–100)	69 (55–84)
Nephelotex (Biopool)	87 (42)	98 (93–100)	65 (62–89)

^a outcome studies available
^b semiquantitative test

high. Nevertheless, recent large series suggest that complete examination of the leg deep vein system without any other exam is safe and effective in managing patients with clinically suspected DVT [25–27]. For example, Elias et al. examined 623 patients of whom 401 (64.4%) were declared without DVT and were followed up for 3 months with a low thromboembolic risk of 0.5% (95% CI: 0.1–1.8%). However, among the 204 patients with DVT, 92 (45%) were distal and most of them would not have been treated (and submitted to the hazards of anticoagulant treatment) with a similarly low 3-month thromboembolic

Table 3. Comparison of diagnostic strategies including proximal only or proximal and distal compression ultrasonography (CUS) for diagnosing deep vein thrombosis (DVT; outcome studies).**Tabelle 3.** Vergleich verschiedener diagnostischer Strategien mit ausschließlich proximaler oder kompletter (proximaler + distaler) Kompressionsultrasonographie (CUS) für die Diagnose der tiefen Venenthrombose (DVT; pragmatische Studien).

Series	Patients (n)	Prevalence of DVT (%)	Proportion of distal DVT (%)	Number of CUS performed per 100 patients (n)	3-month thromboembolic risk [% (95% CI)] ^a
Proximal CUS only					
Cogo et al. [21]	1,702	24	–	176	0.7 (0.3–1.2)
Bernardi et al. [22]	946	28	–	109	0.4 (0–0.9)
Wells et al. [14]	593	16	–	128	0.6 (0.1–1.8)
Perrier et al. [13]	474	24	–	73	2.6 (0.2–4.9)
Kraaijenhagen et al. [24]	1,756	22	–	121	0.6 (0.1–1.6)
Proximal and distal CUS					
Elias et al. [25]	623	36	45	100	0.5 (0.1–1.8)
Schellong et al. [26]	1,646	17	56	100	0.3 (0.1–0.8)
Stevens et al. [27]	445	14	31	100	0.8 (0.2–2.3)

^a during 3-month follow-up in patients left untreated

risk if only a proximal CUS had been performed [25]. Schellong et al. reported a similar 3-month thromboembolic risk of 0.3% in a series of 1,646 patients of whom 275 were positive for DVT but, again, 154 DVTs (56%) were distal, suggesting a risk of overdiagnosis and overtreatment [26]. Table 3 offers a comparison of the results obtained with the simplified or complete lower-limb venous CUS.

Ascending Phlebography

Ascending phlebography is still considered the diagnostic standard for diagnosing DVT but it is invasive, costly, and not devoid of risk. It consists in the injection of iodinated contrast dye in a superficial foot vein with sequential radiograms of the leg in order to follow the dynamic course of the contrast in the veins. Tourniquets can be used to force the dye into the deep veins but their use is controversial. The documentation is adequate when images are obtained in different views, and a filling defect surrounded by contrast is characteristic of a fresh thrombus.

Sequential Diagnostic Strategies for Suspected DVT

Several noninvasive strategies have been reported to have a high sensitivity for diagnosing DVT [3]. Some rely on serial proximal CUS of proximal veins (common femoral, superficial femoral, and popliteal veins). The rationale for repeating CUS after 1 week in patients in whom it was initially negative is the detection of the rare proximal extension of the distal DVTs that were not searched for. Since the yield of repeat CUS after 1 week is very low [14, 21, 22], CUS has been

combined with a clinical prediction rule and/or DD measurement to lower the number of necessary repeat compression sonograms [14, 21, 22, 28, 29]. In another strategy, single CUS was restricted to patients with a DD concentration above a critical cutoff level (500 µg/l), thereby avoiding about 30% of CUS exams [13]. All these strategies are associated with a low (about 2% or less) 3-month thromboembolic risk, which is similar to that observed in suspected patients left untreated following a normal phlebogram [30]. In a randomized study, Wells et al. compared the clinical outcome in 530 patients who underwent CUS (control group) and 566 patients who underwent DD testing followed by CUS unless the DD test was negative and the patient was considered at low clinical probability [31]. The 3-month thromboembolic risk among patients in whom the initial diagnostic strategy had ruled out DVT was 0.4% in the DD group, compared with 1.4% in the control group. The difference did not reach statistical significance but the use of DD resulted in a highly significant reduction in the use of CUS, since 39% of patients did not require ultrasound imaging. Overall, modern diagnostic approach to DVT is based upon evaluation of clinical probability, DD measurement and CUS. Figure 1 suggests a possible diagnostic algorithm for suspected DVT and the interested reader may find a complete description of all diagnostic strategies used in the literature in a recent review [32].

Treatment of Deep Vein Thrombosis Medical Treatment

The aims of treatment are to relieve symptoms, reduce the risk of PE, and prevent postthrombotic syndrome (PTS) and recurrent VTE. Anticoagulation is

the mainstay of treatment of DVT. The initial treatment of acute DVT is based upon administration of LMWH or unfractionated heparin (UFH).

The Seventh ACCP (American College of Chest Physicians) Consensus on Antithrombotic and Thrombolytic Therapy recommends treating patients with a high clinical probability of DVT while awaiting the results of diagnostic tests (grade 1C+). However, as the prevalence of DVT in patients with an intermediate clinical probability of DVT may be as high as 20–30%, a more appropriate option would be to begin anticoagulation while awaiting outcome of diagnostic tests also in patients with an intermediate clinical probability of DVT. In most cases, warfarin can be started on the 1st day. LMWH or UFH should be continued for at least 5 days and until the International Normalized Ratio (INR) is within the therapeutic range (i.e., between 2 and 3) on at least two dosages at an interval of 24 h.

LMWH has become the standard of care for the initial treatment of DVT as it is as effective and safe as UFH but is more practical to use and has a more favorable side effects' profile. Many available LMWHs may be used once or twice daily. Contrarily to UFH, laboratory monitoring is not mandatory in the vast majority of patients treated with LMWHs. Some exceptions are patients with renal impairment, obesity and pregnancy. As LMWHs are excreted by the kidney, they should not be used in patients with a creatinine clearance of < 30 ml/min. In these patients using UFH is recommended.

The predictable anticoagulant response of LMWHs allows out-of-hospital treatment in more than 80% of patients with acute DVT. Outpatient therapy offers reduced economic costs to patients and the health-care system as a result of decreased resource utilization. Once or twice daily dosing and fixed dosages combined with a well-planned program of patient education and professional support offer convenience to patients while enhancing successful adherence to home treatment. In 1996, the results of a meta-analysis of 20 randomized controlled studies comparing multiple clinical outcomes of LMWH and UFH [33] showed that treatment with LMWH had a more favorable benefit-to-risk ratio than treatment with UFH. More recently, two other meta-analyses showed that treatment with LMWH is at least as effective as UFH in terms of risk of major bleeding, PE, and recurrent DVT [34, 35]. The safety and efficacy profiles of LMWHs, such as dalteparin, enoxaparin, nadroparin, logiparin and tinzaparin, are well established. Recently, Kearon et al. demonstrated that fixed-dose weight-adjusted subcutaneous UFH was as effective and safe as LMWH in patients with acute VTE and was suitable for outpatient treatment [36], a finding that might impact the management of acute

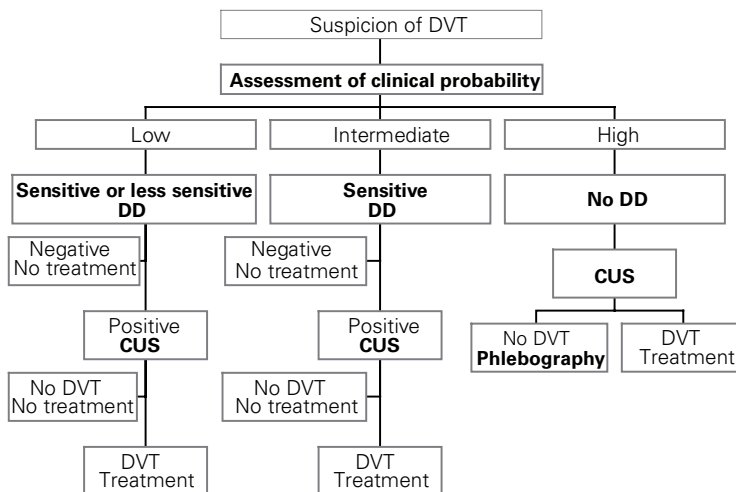


Figure 1. Diagnostic algorithm for clinically suspected deep vein thrombosis (DVT). Sensitive D-dimer assay means at least 95% sensitivity for the presence of DVT. CUS: lower limb venous compression ultrasonography; DD: D-dimer measurement.

Abbildung 1. Diagnostischer Algorithmus bei klinischem Verdacht auf tiefe Venenthrombose (DVT). Ein sensitiver D-Dimer-Test bedeutet eine Sensitivität von mindestens 95% für die Anwesenheit einer DVT.

CUS: venöse Kompressionsultrasonographie; DD: D-Dimer-Bestimmung.

VTE because UFH is much less expensive than LMWH, at least in some countries.

Thrombolysis and Invasive Treatment

Systematically administered or catheter-directed thrombolysis should not be routinely used in patients with lower-limb DVT and should be confined to patients requiring limb salvage (phlegmasia coerulea dolens). Catheter extraction, fragmentation or surgical thrombectomy should not be used in routine for the treatment of DVT [37]. However, these options may be discussed in young patients with massive isolated iliofemoral DVT at risk of limb gangrene secondary to massive, proximal venous occlusion.

Duration and Intensity of Anticoagulant Long-Term Treatment

The duration of anticoagulant treatment following a venous thromboembolic episode has always been a matter of debate with recommended durations following a first episode varying between 3 months and 1 year, depending upon the weight given to the respective risks of recurrence and bleeding induced by the treatment [38]. Since VTE is a recurrent disease, anticoagulation should ideally last forever. However, the risk of recurrence diminishes with time and the risk of bleeding, after an initial peak, is rather constant over time. Thus, there must be some time point

for which the bleeding risk exceeds the protective effect of the treatment, which should then be stopped [37].

As already mentioned, there is no consensus for duration of anticoagulation for all situations clinicians may be faced with. In practice, after an initial course of 3–12 months of conventional-intensity warfarin, the prolongation of anticoagulation treatment may be tailored on an individual basis. Some indications for long-term anticoagulation are active neoplasia, antiphospholipid syndrome with previous VTE and persistent antiphospholipid antibodies, and some congenital thrombophilias as severe antithrombin or protein C deficiency [37]. Maintaining long-term anticoagulation may be discussed as well in presence of two or more previous idiopathic VTEs, even if the evidence supporting this attitude are scarce. Obviously, the necessity of maintaining long-term anticoagulation should be reassessed annually, in particular to weight the possibility of new clinical events associated with an increased hemorrhagic risk, which could limit the benefit-risk ratio of long-term anticoagulant treatment. The option of prolonging the treatment with low-intensity warfarin (for example INR between 1.5–2) may be useful at least in selected patients at higher risk of bleeding [39, 40]. A shorter period of anticoagulation (3 months) is accepted for VTE occurring after a transient risk factor like surgery or trauma [37].

Compression Treatment of DVT in the Acute and Chronic Phases

The PTS develops in 20–50% of patients after symptomatic DVT and is the most common long-term complication of DVT [41–43]. Patients with PTS experience pain, heaviness, swelling, cramps, itching or tingling in the affected limb. Symptoms may be present in various combinations and may be persistent or intermittent. Symptoms are usually aggravated by standing or walking and improve with resting, leg elevation any lying down. In severe cases, skin changes and ulcers may develop. The frequency of PTS is likely to be reduced by preventing DVT with the use of effective thromboprophylaxis in high-risk patients and settings. However, once DVT has developed, the use of compression stockings for 2 years after DVT appears to reduce the incidence and severity of PTS.

To date, three trials have evaluated the effectiveness of long-term use of elastic stockings for the prevention of PTS after acute DVT. The first study by Brandjes et al. randomly allocated 194 patients to daily use of a 30- to 40-mmHg knee-length elastic compression stockings for at least 2 years or no stockings [44]. Use of elastic compression stockings

resulted in a decrease from 47% to 20% of mild/moderate PTS and a decrease from 23% to 11% of severe PTS. A second study by Ginsberg et al. compared the effect of active stockings to sham stockings to prevent PTS after proximal DVT in patients who had venous valvular incompetence but no clinical PTS 1 year after the index event [45]. This study showed no benefit of elastic stockings as none (0%) of the 24 patients allocated to the active stockings developed PTS, compared with one (4.4%) of 23 patients treated with sham stockings ($p = 0.49$). Another trial by Prandoni et al. evaluated the effectiveness of 30- to 40-mmHg elastic stockings versus no stockings in 180 patients after a first symptomatic proximal DVT [46]. The 2-year cumulative incidence of PTS, evaluated by using the Villalta's score was 25% in the stocking group compared with 49% in the control group ($p = 0.011$). Lastly, a meta-analysis pooled these three studies and reported an overall 54% relative risk reduction in PTS with the use of stockings [47]. Even if the lack of blinding in the two positive studies reduces the confidence in the results as scores used for the evaluation of PTS are highly subjective and even if some questions such as the optimal length and strength of compression remain unanswered, initiation of compression therapy has to be considered an important point in the care of acute DVT [48].

Treatment of Calf DVT

In spite of the reassuring data obtained from the outcome studies using proximal CUS (Table 3), recent consensus conferences, including that of the ACCP, still recommend to treat calf DVT with anticoagulants for a period of 3 months [37]. Nevertheless, opting for a 3-month anticoagulant treatment in the presence of a distal DVT raises several problems. First, series based on serial ultrasonography indicate that only a small fraction of distal DVTs extends proximally in medical outpatients. Indeed, the rate of proximal DVTs detected by the repeated ultrasound varies from 0.9% to 5.7% [14, 21, 22, 24]. Second, the randomized 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 [49]. Third, muscle vein thromboses (i.e., gemellar and soleal vein thrombosis) are probably less dangerous than thrombosis of the deep distal veins (i.e., peroneal and tibial posterior veins). Macdonald et al. showed, in a prospective study where muscular thromboses were not treated but followed by ultrasonography, that only 3% of muscular thromboses extended in the popliteal vein [50]. This suggests that the vast majority of muscular vein thromboses need either 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. Therefore, the 1A grade of recommendation delivered by the ACCP consensus conference suggesting a similar treatment for proximal DVTs and calf DVTs [37] seems not to be supported by the available evidence.

Conclusion and Perspectives

Venous thromboembolic disease encompasses a wide spectrum of conditions with various severity and prognostic implications. DVT is an important cause of morbidity and mortality, and as the awareness of this pathology has increased during the last 2 decades, the prevalence of the disease in suspected populations has dramatically decreased. Recent studies have shown that algorithms combining simple diagnostic tests may provide a safe diagnostic approach to suspected DVT, with a 3-month thromboembolic risk similar to or lower than that reported after a normal phlebography, the accepted gold standard. Assessment of clinical probability, done empirically or by a prediction rule, has shown to be highly useful and allows identifying patients with a low prevalence of the disease, who can be investigated by noninvasive diagnostic tools. Plasma DD measurements have been widely validated and allow to rule out the disease with an acceptable safety in selected patients. CUS has become the cornerstone diagnostic test for DVT and its diagnostic performances are excellent in the case of symptomatic proximal DVTs. Many algorithms combining in various order these last three tests have been validated, and may be safely used in clinical practice. In spite of these advances, the field faces several challenges for the future. One challenge will consist in establishing which conditions need to be treated with anticoagulant drugs, a question that pertains essentially to calf or muscle vein thrombosis. Its answer will have consequences for diagnostic algorithms.

As a matter of fact, LMWHs have considerably simplified the initial management of DVT and allowed out-of-hospital treatment. However, their porcine origin is still a concern. Several new, totally synthetic, orally active anticoagulant compounds, such as direct thrombin or factor Xa inhibitors, are presently being tested in clinical studies and could profoundly modify DVT treatment in the near future.

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