Clinical aspects of venous thromboembolism in special patient populations

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Citation for published version (APA):
Upper extremity deep vein thrombosis

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Published in “Current management of venous diseases” (Book), Springer, 2016.
Abstract

Upper extremity deep vein thrombosis (UEDVT) accounts for up to 10% of all deep vein thrombi. The incidence is increasing, which is mostly due to extensive use of central venous catheters (CVCs). UEDVT often presents with unilateral swelling and pain, but may be asymptomatic. Several factors increase the risk of UEDVT, of which cancer and CVCs are the strongest risk factors. To prevent acute complications and long-term sequelae of UEDVT, such as pulmonary embolism and the post-thrombotic syndrome, a prompt diagnosis and effective and safe therapy is crucial. Objective imaging through venography or compression ultrasonography is at present the cornerstone of diagnosis, despite its moderate efficiency. Current treatment options for UEDVT are anticoagulant therapy, thrombolytic therapy, mechanical catheter interventions, first rib resection in case of thoracic outlet syndrome, and vena cava filter placement. Routine thromboprophylaxis in patients with a CVC is currently not recommended.
Introduction

Upper extremity deep vein thrombosis (UEDVT) is a disease which was first described in the late nineteenth century by Paget and von Schroetter (1,2). The condition accounts for approximately 4% to 10% of all deep vein thrombi, with an estimated incidence of 3.6 per 100,000 patient-years (3). UEDVT is an increasingly frequent clinical problem, mainly due to the widespread use of central venous catheters (CVCs) which carry a substantial risk of thrombosis (3,4). It may involve the radial, ulnar, brachial, axillary, subclavian, internal jugular and brachiocephalic veins, but most often occurs in the subclavian or axillary veins; frequently more than one venous segment is affected (Figure 10.1) (5–11). Deep vein thrombosis (DVT) of the radial, ulnar and brachial DVT are considered distal UEDVT, whereas DVT in the axillary or more proximally located veins is referred to as proximal UEDVT. As UEDVT may lead to loss of venous access or pulmonary embolism (PE) in the acute phase, and is associated with serious long-term complications such as the post-thrombotic syndrome (PTS), prompt diagnosis and treatment is warranted. At present, objective imaging is the cornerstone of diagnosis despite its moderate efficiency. Several diagnostic strategies to improve diagnostic efficacy have been proposed and tested, but which strategy can most safely and effectively exclude UEDVT remains yet to be determined.

In the absence of direct evidence, current treatment recommendations are largely extrapolated from studies on lower extremity DVT, since for UEDVT only small, observational studies are available. In this chapter we discuss the current understanding on the clinical characteristics, risk factors, diagnosis, management, prognosis and prevention of UEDVT.

**Figure 10.1** Deep veins that may be involved in upper extremity deep vein thrombosis.
Chapter 10

**Symptoms and signs**

Patients with UEDVT most often present with unilateral swelling and discomfort or localized pain (4,8,12–14). Other symptoms and signs that have been described are weakness, paraesthesia, heaviness, low-grade fever, visible collateral veins, erythema, a palpable cord, cyanosis and warmth (Table 10.1) (8,12,15–18). The majority of UEDVT associated with a CVC or pacemaker remain subclinical, as most cases are discovered during the work-up of a dysfunctional catheter or PE (19–21). Concomitant symptomatic PE is present in 3% to 12% of all patients with UEDVT (6,7,22–27), which is less than in patients with lower extremity DVT, in which prevalences of around 30% have been reported (22,27).

**Table 10.1** Possible symptoms and signs of upper extremity deep vein thrombosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prevalence in patients with UEDVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral edema or swelling</td>
<td>70%-100% (4,8,12,13,77)*</td>
</tr>
<tr>
<td>Discomfort or localized pain</td>
<td>34%-83% (4,8,12,13,77)*</td>
</tr>
<tr>
<td>Weakness</td>
<td>NR</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>NR</td>
</tr>
<tr>
<td>Heaviness</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td>77% (77)</td>
</tr>
<tr>
<td>Warmth</td>
<td>36%-52% (12)</td>
</tr>
<tr>
<td>Erythema or skin color change</td>
<td>3%-47% (4,13)*</td>
</tr>
<tr>
<td>Visible collateral veins</td>
<td>20%-34% (12)*</td>
</tr>
<tr>
<td>Palpable cord</td>
<td>3%-12% (8)*</td>
</tr>
<tr>
<td>Low-grade fever</td>
<td>5%*</td>
</tr>
<tr>
<td><strong>No symptoms or signs</strong></td>
<td>5% (4)</td>
</tr>
</tbody>
</table>

Abbreviations: UEDVT = upper extremity deep vein thrombosis; NR = not reported
* Including own data from a cohort of 104 consecutive patients with confirmed UEDVT, previously enrolled in a prospective diagnostic management study (7)

**Risk factors**

UEDVT is subdivided into primary and secondary UEDVT, based on the pathogenesis. Primary UEDVT represents 20% to 50% of all cases, and includes effort-related thrombosis (also known as the Paget-Schroetter syndrome) in combination with the thoracic outlet syndrome (TOS), and idiopathic thrombosis. The majority of UEDVT are secondary to a predisposing risk factor (3,9,28–31). The risk factors most strongly associated with
Unsuspected pulmonary embolism in cancer patients

**Table 10.2** Risk factors for upper extremity deep vein thrombosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio (compared to healthy controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>18.1 (28)</td>
</tr>
<tr>
<td>Surgery of the upper extremity</td>
<td>13.1 (28)</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>9.7 (4)</td>
</tr>
<tr>
<td>Immobilization (plaster cast)</td>
<td>7.0 (28)</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>2.8 (28)</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>2.6–6.2 (28,78–80)</td>
</tr>
<tr>
<td>Trauma of the upper extremity</td>
<td>2.1 (28)</td>
</tr>
<tr>
<td>Any surgery lasting more than 1 hour</td>
<td>1.7 (81)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>1.2–2.9 (28,79,82)</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism

UEDVT are cancer and the presence of a CVC. Other risk factors include pacemakers, previous venous thromboembolism (VTE), a positive family history of VTE, arm surgery or trauma, immobilization, the use of estrogens, and thrombophilia (Table 10.2).

**The Paget-Schroetter syndrome**

The Paget-Schroetter syndrome accounts for 10% to 20% of all UEDVT, and mainly occurs in young, otherwise healthy individuals who encounter repetitive or strenuous arm movements (10,31–33). It has been mostly associated with sport activities such as baseball, swimming, weight lifting and wrestling (34,35), but also with playing the violin for prolonged periods of time. The pathogenesis of the Paget-Schroetter syndrome is not entirely elicited, but it is thought that venous TOS plays a key role. Venous TOS is characterized by compression of the subclavian vein, usually caused by either congenital or acquired variations in bone and muscle anatomy (36,37). This renders the subclavian vein more susceptible to trauma. Repeated trauma then leads to intimal hyperplasia, inflammation and perivascular fibrosis, which may eventually cause venous thrombosis (38).

**Central venous catheters**

Common indications for CVC placement are the administration of chemotherapy, parenteral nutrition and prolonged intravenous antibiotic treatment. It is estimated that over 5 million CVCs are inserted annually in the United States (39). CVC-related UEDVT accounts for up to 70% of all secondary UEDVT (8,24,31). The high risk of CVC-associated UEDVT is mainly due to vessel wall damage following insertion and infusion of irritating substances, and to impeded blood flow through the vein across the catheter. The incidence of symptomatic and asymptomatic CVC-related UEDVT lies around 2% to 6%
and 11% to 19%, respectively (17,40). Baseline factors that increase the UEDVT risk are subclavian vein insertion, improper positioning of the catheter tip, and multiple lumen catheters (Table 10.3) (41). Peripherally inserted central catheters are associated with a higher UEDVT risk than implanted ports (odds ratio [OR] 2.55, 95% confidence interval [CI] 1.54–3.24), especially in critically ill (incidence 13.9%, 95%CI 7.7–20.1) and cancer patients (incidence 6.7%, 95%CI 4.7–8.6) (41,42).

Table 10.3 Central venous catheter-specific risk factors for upper extremity deep vein thrombosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of catheter</strong></td>
<td></td>
</tr>
<tr>
<td>• PICC</td>
<td>1*</td>
</tr>
<tr>
<td>• Implanted port</td>
<td>0.4 (41)</td>
</tr>
<tr>
<td><strong>Number of lumina</strong></td>
<td></td>
</tr>
<tr>
<td>• Single lumen</td>
<td>1*</td>
</tr>
<tr>
<td>• Double lumen</td>
<td>1.3–3.5 (41,42,81)</td>
</tr>
<tr>
<td>• Triple lumen</td>
<td>3.3–39.5 (41,42,81)</td>
</tr>
<tr>
<td><strong>Multiple insertion attempts</strong></td>
<td>1.1† (42)</td>
</tr>
<tr>
<td><strong>Insertion site</strong></td>
<td></td>
</tr>
<tr>
<td>• Upper arm veins</td>
<td>1*</td>
</tr>
<tr>
<td>• Subclavian vein</td>
<td>2.2 (41)</td>
</tr>
<tr>
<td>• Internal jugular vein</td>
<td>1.6† (41)</td>
</tr>
<tr>
<td><strong>Catheter tip positioning</strong></td>
<td></td>
</tr>
<tr>
<td>• Proper positioning</td>
<td>1*</td>
</tr>
<tr>
<td>• Improper positioning</td>
<td>1.9 (41)</td>
</tr>
</tbody>
</table>

CI: confidence interval; PICC: peripherally inserted central catheter
† Unadjusted for other risk factors
* Reference category
‡ Confidence interval crosses 1

**Cancer**

Approximately 40% of all patients with UEDVT have active cancer; it is one of the strongest risk factors for the development of UEDVT (adjusted OR 18.1, 95%CI 9.4–35.1). The presence of distant metastases increases the risk even further, for an OR of 11.5 (95%CI 1.6–80.2) compared to cancer patients without metastases. Cancer and CVCs often coincide (22), as a substantial proportion of cancer patients require a CVC for the administration of chemotherapy (40). The presence of a CVC increases the UEDVT risk in patients with active cancer approximately 2-fold (OR 43.6, 95%CI 25.5–74.6) (28).
Diagnosis

An accurate diagnosis of UEDVT is important, as appropriate treatment can reduce the clinical burden and prevent complications in the acute phase, such as PE. The prevalence of UEDVT in patients with a clinical suspicion of UEDVT varies from 10% to 45% in several cohort studies, which might be explained by differences in study design and the proportions of cancer patients, CVCs and the number of inpatients (Table 10.4) (7,12,43,44). In patients with a CVC, the prevalence of UEDVT was 53% in one study (7), compared to only 18% in patients without a CVC (p < 0.01). These figures were 31% and 23% for cancer and non-cancer patients, respectively (p = 0.07; van Es N., submitted data).

Table 10.4 Prevalence of upper extremity deep vein thrombosis and associated risk factors in consecutive patients with a clinical suspicion of upper extremity deep vein thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Constans (12)</th>
<th>ARMOUR (7)</th>
<th>Sartori (44,83)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1</td>
<td>Cohort 2</td>
<td>Cohort 3</td>
</tr>
<tr>
<td>Patients, n</td>
<td>140</td>
<td>103</td>
<td>214</td>
</tr>
<tr>
<td>UEDVT confirmed, n (%)</td>
<td>50 (36)</td>
<td>46 (45)</td>
<td>65 (30)</td>
</tr>
<tr>
<td>Study design</td>
<td>Single center</td>
<td></td>
<td>Multicenter</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>52</td>
<td>54</td>
<td>NR</td>
</tr>
<tr>
<td>CVC (%)</td>
<td>61</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td>Inpatient (%)</td>
<td>100</td>
<td>100</td>
<td>53</td>
</tr>
</tbody>
</table>

UEDVT: upper extremity deep vein thrombosis; CVC: central venous catheter, NR: not reported

Venography is the gold standard to diagnose UEDVT, as it visualizes the entire deep vein system of the upper extremity, but it is invasive, expensive, and involves the use of contrast, which may cause complications including renal failure and allergic reactions. Due to these disadvantages, venography has been largely replaced in clinical practice by compression ultrasonography, which is non-invasive, relatively cheap, and easy to perform (18). In a systematic review identifying 9 studies on the role of compression ultrasonography in the diagnosis of UEDVT, the overall sensitivity was 97% (95%CI 90–100%), with a specificity of 96% (95%CI 87–100%) (45). The presence of the clavicle may hinder evaluation of the middle part of the subclavian vein, and in case of indeterminate compression ultrasonography results, venography may provide a definitive answer. Other diagnostic options include computed tomography (CT) angiography and magnetic resonance angiography (MRA), which are both non-invasive. However, both have only been evaluated in studies with very few patients with a clinical suspicion of UEDVT, and the diagnostic performance of both modalities is therefore unclear (46,47).
Several attempts have been made to improve the diagnostic process in patients with a clinical suspicion of UEDVT. Constans and colleagues developed a clinical decision rule, incorporating four items (Table 10.5) (12). If the total score is one or less, UEDVT is deemed unlikely, whereas if the total score is two or higher, the diagnosis is likely. The prediction of UEDVT based on this score was consistent in three study samples, with prevalences of 64 to 70% in patients with a total score indicating ‘UEDVT likely’, and 9 to 13% in those with a total score indicating ‘UEDVT unlikely’, suggesting that this score can be a valuable tool in a diagnostic algorithm (12).

The diagnostic value of D-dimer has been tested in two studies, one including 52 patients of whom 15 (29%) had UEDVT, and the other including 239 patients, of whom 24 (10%) were diagnosed with UEDVT (43,48). Both studies applied a cut-off value of 500 ng/mL. The sensitivity was high in both studies with 100% (95%CI 78–100%) and 92% (95%CI 73–99%) respectively, whereas the specificity was low (14%, 95%CI 4–29% and 60%, 95%CI 52–67%, respectively). These figures were similar for cancer patients and patients with a CVC (43,48).

Recently, a multicenter, international, prospective diagnostic management study evaluated an algorithm consisting of the Constans score, d-dimer testing and compression ultrasonography in consecutive patients with a clinical suspicion of UEDVT (7). In total, 406 patients were included, and the algorithm was feasible in 390 (96%). UEDVT was confirmed in 103 patients (25%). In 87 patients (21%; 95%CI 17–25%), ultrasonography could be withheld. One patient in which UEDVT initially was excluded, developed a UEDVT during 3 months follow-up, for an overall failure rate of the algorithm of 0.4% (95%CI 0–2.2%). In another study, 483 patients with a clinical suspicion of UEDVT all underwent immediate compression ultrasonography, and were followed for 3 months prospectively. The failure rate, defined as the rate of recurrent VTE, was 0.6% (95%CI 0.2–2.2%) for single ultrasonography and 0.2% (95%CI 0.1–1.7%) for serial ultrasonography. Of note, the prevalence of UEDVT was relatively low in this cohort (13%) (44).

While there have been important improvements in the field, the best diagnostic strategy in patients with a clinical suspicion of UEDVT still remains to be determined. Hence,

<table>
<thead>
<tr>
<th>Item</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous material present*</td>
<td>+1</td>
</tr>
<tr>
<td>Localized pain</td>
<td>+1</td>
</tr>
<tr>
<td>Unilateral edema</td>
<td>+1</td>
</tr>
<tr>
<td>Other diagnosis at least as plausible</td>
<td>-1</td>
</tr>
</tbody>
</table>

* Central venous catheter or pacemaker thread

If the total score is ≤ 1, upper extremity deep vein thrombosis is unlikely; if the total score is ≥ 2, upper extremity deep vein thrombosis is likely.
at present, objective imaging remains the cornerstone of UEDVT diagnosis. D-dimer testing may help to reduce the number of patients who require imaging, although the efficiency of the test appears moderate in this population with high prevalences of cancer and CVCs. The use of an algorithm has been shown to be efficient and safe, but needs to be validated prospectively before it can be implemented in clinical practice. Furthermore, improvement of the algorithm appears to be desirable, for example by applying age-adjusted d-dimer cut-off values (van Es N., in press). In patients with a CVC and a suspicion of UEDVT direct imaging seems justified, as only two examinations have to be performed to detect one UEDVT.

**Treatment**

In the acute phase of UEDVT, the goal is to relieve acute symptoms and prevent complications, such as the loss of venous access or development of PE. The long term goals of treatment are mainly the prevention of recurrent VTE, including fatal PE, and the development of PTS. Treatment options for UEDVT are thrombolytic therapy, anticoagulant therapy, mechanical catheter interventions, first rib resection, and vena cava filter (VCF) placement. No randomized controlled trials have evaluated any of these therapies in patients with UEDVT. Therefore, treatment recommendations by the major guidelines are largely extrapolated from studies on DVT of the leg, and are only based on small observational studies in UEDVT patients (49).

**Thrombolytic therapy**

Thrombolytic therapy may improve early and late venous patency in patients with UEDVT (50–54), but whether it lowers the risk of recurrent VTE or development of PTS remains unknown. The American College of Chest Physicians (ACCP) guideline suggests that thrombolysis is considered only in patients with severe symptoms for less than 14 days with a good functional status, a life expectancy of at least one year, and a low risk of bleeding (49). Data on the use of thrombolytic therapy for UEDVT is limited but suggests a high risk of major bleeding of up to 17% when systemically administered (51,53,54). Therefore, if thrombolysis is applied, catheter-directed thrombolysis is recommended over systemic thrombolysis, based on the assumption that this is associated with lower bleeding risk (49).

**Anticoagulant therapy**

In patients with lower extremity DVT, low-molecular-weight heparin (LMWH) has a superior efficacy and better safety compared to unfractionated heparin (UFH) for the initial period of treatment (i.e. the first 5 to 10 days) (55). In addition, four observational
studies that included a total of 209 patients with UEDVT receiving LMWH, reported low recurrence and major bleeding rates (26,56–58). Based on these data, LMWH is the preferred anticoagulant for the initial phase of UEDVT treatment (Figure 10.2). UFH is reserved for patients with contraindications to LMWH such as severe renal failure (49).

For the long-term treatment of UEDVT, i.e. after the initial phase of 5 to 10 days, treatment options besides LMWH are vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs). VKA have been the standard method of anticoagulation for decades, but the use of DOACs is emerging since large trials have shown that they are as effective as VKA for the treatment of acute symptomatic lower extremity DVT and PE, with a significant reduction in major bleeding events (59). Extrapolating from trials investigating these drugs for the treatment of DVT of the leg or PE, both can be considered for long-term UEDVT treatment. LMWH may be prescribed but the daily injections are cumbersome and painful for many patients, and hypersensitivity skin reactions are often seen. Despite these disadvantages, the cornerstone of treatment in cancer patients is LMWH, based on a superior efficacy and similar safety profile compared to VKA in cancer patients with lower extremity DVT and PE (60,61).
Treatment duration

All patients with proximal UEDVT (i.e. DVT of the axillary or more proximally located veins) are recommended to be treated with a therapeutic dose of anticoagulants for at least 3 months (Figure 10.2). If UEDVT is not associated with a CVC but is associated with active cancer, patients should receive anticoagulation as long as cancer is active or the patient is receiving chemotherapy. In non-cancer patients with non-CVC associated UEDVT, 3 months of treatment is recommended.

If the UEDVT is CVC-associated, the CVC should not be removed if it is functioning well and there is an on-going need for it. This recommendation is in part based on the fact that many patients still require central venous access, and insertion of another CVC will increase the thrombotic risk as well. Furthermore, an observational study showed no benefit of CVC-removal in 58 of 112 patients (52%) with symptomatic CVC-related thrombosis. In total, 4 patients failed to show resolution of their presenting symptoms, all of whom had their CVC removed at the time of UEDVT (62). In another, prospective study including 74 patients with acute symptomatic CVC-related UEDVT in which the catheter remained in place, there were no recurrent VTE during 3 months of anticoagulant therapy (56). According to the ACCP guideline, anticoagulation should be given as long as the CVC remains in place. This is similar for cancer and non-cancer patients. If the CVC is removed, only 3 months of treatment is recommended, regardless of the presence of cancer. There are no data to guide whether CVC removal should be preceded by anticoagulant therapy (49). There is some debate on the safety of cessation of therapy in patients in whom the CVC is removed, but who still have active cancer after 3 months. In a recent retrospective study the cumulative probability of recurrent VTE was 22.2% in patients with active cancer after cessation of anticoagulant therapy, compared to 2.3% in those in remission (p = 0.02 by log-rank test) (63). Another study reported a recurrent VTE rate after 3 months of 7.7% in cancer patients with CVC-related UEDVT, compared to 4.4% in cancer patients with non-CVC related UEDVT (22). These data suggest that patients with active cancer with CVC-related UEDVT in whom the CVC is removed, may benefit from anticoagulation beyond 3 months.

For distal UEDVT, there significant uncertainty on the benefits of anticoagulation, as it is thought that complications occur less often and are less severe in case of distal UEDVT as compared to proximal UEDVT. Therefore, conservative treatment with close surveillance to detect UEDVT extension, a prophylactic dose of anticoagulation, or a shorter course of treatment are options alternative to full therapeutic anticoagulation. If distal UEDVT is symptomatic, associated with a CVC (with the CVC remaining in situ) or with cancer, 3 months of therapeutic dose anticoagulation is favored, unless there is a high bleeding risk (49).
**Chapter 10**

**Mechanical catheter interventions**
Mechanical interventions include clot aspiration, fragmentation, thrombectomy, percutaneous transluminal angioplasty, and stent placement. These techniques are mostly used in combination with catheter directed thrombolysis. Stents have been associated with high rates of complications such as stent fracture and rethrombosis in the presence of TOS (64,65).

**First rib resection**
In patients with UEDVT and TOS, surgical decompression through first rib resection has been advocated (49). No randomized trials have evaluated the efficacy and safety of first rib resection in the resolution of acute complaints and prevention of long term sequelae such as a recurrent VTE and PTS. This intervention should probably be limited to patients with severe, persistent symptoms and residual subclavian vein stenosis that does not resolve despite adequate anticoagulant therapy, and should be reserved for centers with sufficient expertise (66).

**Vena cava filter**
In patients with a contraindication for anticoagulant therapy, placement of a VCF may be considered. In a review, reporting on a total of 209 superior VCF placements in patients with UEDVT, complications occurred in 3.8% of the cases, including cardiac tamponade, aortic perforations and a pneumothorax (67). The use of VCF should be limited to experienced centers.

**Other therapies**
The use of compression stockings to prevent PTS after UEDVT has not been investigated, and the ACCP suggests against its routine use (49).

**Prognosis**
On the long term, UEDVT can be complicated by recurrent VTE, PTS, bleeding during anticoagulation, and death. To date, mostly small studies with methodological shortcomings have evaluated the long term clinical outcome of UEDVT. A systematic review of all available studies on this topic reported an average incidence of recurrent VTE of 3% to 4% during anticoagulant therapy. After cessation of treatment, the annual incidence of recurrence lies around 4% (68). PTS after UEDVT seems to occur infrequently, and complaints are mostly mild (31,69). Compared to DVT of the leg, the incidences of recurrent VTE and of PTS after UEDVT seem relatively low (26,27,31,69,70).
The recurrence risk in patients with CVC-related UEDVT was reported in two prospective studies; one observed an incidence of 7 per 100 patient-years during anticoagulant therapy, which decreased to 3.4 per 100 patient-years after cessation of treatment (71). Another study observed recurrent VTE in 4.4% of the patients during 3 months of anticoagulant therapy (72). Of note, in both studies no information was available on catheter removal. Cancer patients with UEDVT appear to have a two-fold higher risk of recurrent VTE compared to non-cancer patients (22,31,68), which is comparable to findings from studies on DVT of the leg or PE (73,74).

In patients receiving a therapeutic dose of anticoagulants, the cumulative incidence of major bleeding is approximately 4% after half a year of treatment (22,31,58,68,75). The mortality rate in patients with UEDVT is high and reflects the high prevalence of underlying cancer. To which extent fatal PE adds to this risk is unclear.

**Prevention**

The prevention of UEDVT has mainly been investigated in patients with indwelling CVCs. A total of six meta-analyses evaluating the efficacy and safety of VKA in the prevention of CVC-related thrombosis showed no overall benefit on the occurrence of symptomatic thrombosis compared to placebo or no treatment (76). Six randomized studies in cancer patients with CVCs found no increased risk of bleeding with LMWH thromboprophylaxis, but also no benefit in preventing CVC-related thrombosis. Routine anticoagulant thromboprophylaxis is therefore not recommended in patients with a CVC by the major international guidelines (49,76). The role of UFH, thrombolitics and heparin-bonded catheters in the prevention of CVC-related thrombosis remains uncertain (41,76). CVCs should only be placed in carefully selected patients in whom the benefits outweigh the risks. As mentioned before, several catheter-specific factors increase the risk of UEDVT, and should be taken into account when placing a CVC (Table 10.3).

**Future directions**

Several aspects related to UEDVT remain unresolved. Future studies need to evaluate what the most effective and safe diagnostic strategy is to confirm or refute UEDVT. Furthermore, in cancer patients with CVC-related UEDVT in whom the CVC is removed, the efficacy and safety of 3 months of anticoagulant therapy versus prolonged treatment should be assessed. Ideally, future studies would include the use of DOACs for the treatment of UEDVT.
Chapter 10

More research is warranted to identify those patients with a CVC in whom the benefits of pharmacological thromboprophylaxis exceed the associated harms, for example by risk stratification. Also, new regimens that are possibly effective and safe in preventing CVC-associated UEDVT, including prophylactic doses of DOACs, should be explored.

Acknowledgments

We would like to acknowledge Marcello Di Nisio for his critical revision of the manuscript for intellectual content.
References


Unsuspected pulmonary embolism in cancer patients

Chapter 10