EXPERT REVIEWS

Treating venous thromboembolism in patients with cancer

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Venous thromboembolism (VTE) is a major cause of morbidity and mortality among patients with cancer. Although much is known about the factors that contribute to VTE risk, pre-emptive therapy in high-risk populations is clearly indicated in only a few clinical situations. Low-molecular-weight heparin is still the recommended class of anticoagulants for cancer-associated VTE. Management of VTE in patients with renal failure, hemorrhagic brain metastases, thrombocytopenia and coagulopathy remains challenging with few safe and effective alternatives. Novel oral agents are currently being investigated and may play a role in the future in the treatment of cancer-associated VTE.

Keywords: anticoagulation • cancer • low-molecular-weight heparin • venous thromboembolism

Venous thromboembolism (VTE) is a complex and common complication of cancer and its treatment [1,2]. VTE affects up to 20% of cancer patients and is one of the major causes of death in these patients [3]. Compared with VTE in patients without cancer, cancer-associated VTE is associated with higher rates of recurrence, bleeding complications associated with anticoagulation therapy and mortality [3,4]. Patients with cancer-associated thrombosis are more likely to have advanced disease and poor prognosis, suggesting that VTE is a marker of more aggressive disease [5].

Risk factors for cancer-associated thrombosis

Cancer is a well-established independent risk factor for VTE, associated with a 4.1-fold increase in VTE [6]. It is estimated that 15–20% of VTE events occur in cancer patients [7]. Factors that increase the risk of VTE among patients with cancer include type of cancer, advanced disease, surgery, chemotherapy and hospitalization.

Metastatic disease at the time of diagnosis is associated with a 1.4–21.5-fold higher risk of VTE compared with localized disease, depending on cancer type. Risk-adjusted models have shown that metastatic disease at the time of diagnosis is the strongest predictor of VTE within the first year of diagnosis [8–13].

VTE is also a common complication of cancer-related surgery and is the most common cause of death at 30 days after surgery [14]. Cancer patients undergoing surgery have twice the risk of postoperative VTE compared with non-cancer patients undergoing the same surgery [15]. Higher rates of postoperative VTE are seen in patients undergoing abdominal surgery in comparison to urologic or gynecologic surgeries. Postoperative VTE is often a late complication of surgery, with 40% of events occurring more than 21 days after surgery [14].

Hospitalization is one of the most significant risk factors for VTE, with a reported incidence between 2 and 7.8% [1,2,16,17]. In the hospitalized setting, the rate of VTE in cancer patients is twice that of non-cancer patients [1]. Predictors of VTE in hospitalized cancer patients include a more recent diagnosis of cancer, cancer site, stage and the type of cancer-directed treatment [17,18]. Among hospitalized cancer patients, those that develop VTE have a 2.1-fold increased risk of death during their hospitalization when compared with patients without VTE [2].

Cancer patients on active therapy are also at increased risk of VTE. In a population-based study identifying risk factors for VTE in the general population, the use of chemotherapy was associated with a 6.5-fold greater risk of VTE compared with a 4.1-fold risk in cancer patients not on chemotherapy [6]. Among antineoplastic treatment, antiangiogenic agents including

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thalidomide, lenalidomide and bevacizumab have been associated with a particularly high risk of VTE.

Thalidomide and lenalidomide are immunomodulatory agents with antiangiogenic and anti-inflammatory properties that are commonly used in combination with dexamethasone or chemotherapy, such as doxorubicin, in the treatment of multiple myeloma. When thalidomide is used in combination with dexamethasone or chemotherapy, the VTE risk has been shown to be between 7 and 34% [19–22]. Lenalidomide in combination with dexamethasone or chemotherapy is associated with an 11% risk of VTE [22–24]. Based on this increased risk, the American Society of Clinical Oncology (ASCO) guidelines recommend the use of low-molecular-weight heparin (LMWH) or adjusted-dose warfarin (International Normalized Ratio [INR] 1.5) in multiple myeloma patients receiving thalidomide or lenalidomide plus dexamethasone and chemotherapy [25]. However, this recommendation is based on nonrandomized studies of multiple myeloma patients on thalidomide- or lenalidomide-based regimens, as well as extrapolation from studies of postoperative thromboprophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer [26–30]. In a recent meta-analysis of multiple myeloma patients receiving thalidomide- or lenalidomide-based regimens, thromboprophylaxis seems to reduce the risk of VTE but no particular thromboprophylaxis strategy demonstrated a clear benefit [19].

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor thereby inhibiting angiogenesis. Bevacizumab, which is currently used in the treatment of a variety of solid tumors, has been associated with a 3–23% increased risk of VTE and 3% increased risk of arterial thrombotic events [31–34]. Gastric and colorectal cancers are associated with the highest risk of thrombosis among bevacizumab-treated patients [35]. However, in spite of a large body of evidence implicating bevacizumab in the increased VTE risk, a recent pooled analysis of patients in randomized Phase II and III studies failed to demonstrate a statistically significant increase in the unadjusted or exposure-adjusted incidence of all-grade VTE for bevacizumab-treated patient versus controls [36].

Predicting the risk of developing VTE

Based on known risk factors, a simple model for predicting chemotherapy-associated VTE in ambulatory cancer patients was developed by Khorana *et al.* [37]. The patient population from this study was previously described as part of the Awareness of Neutropenia in Chemotherapy Study Group Registry, an observational study of cancer patients initiating a new chemotherapy regimen [38]. The study included patients with breast, colorectal, lung, gynecologic, gastric, pancreatic and lymphoma who were to receive systemic chemotherapy. Other cancer sites made up the 10% of remaining patients. A derivation cohort of 2701 patients was used to develop the risk model, and an independent cohort of 1365 patients was used to validate the model. The five predictive variables identified include cancer site, elevated prechemotherapy platelet count, anemia or use of red blood cell growth factors, elevated prechemotherapy leukocyte count and elevated BMI. Very-high-risk cancer sites (pancreatic and gastric cancer) made up 2% of the derivation cohort and 1.4% of the validation cohort. Over a median follow-up period of 73 days, the rates of VTE in the derivation and validation cohorts, respectively, were 7.1 and 6.7% in patients with a risk score ≥3 out of 6 points, 1.8 and 2% in those with a score of 1–2, and 0.8 and 0.3% in those with a score of 0 [37].

This risk model was subsequently validated in another cohort of cancer patients and expanded with two additional laboratory markers, soluble P-selectin (sP-selectin) and D-dimer (Table 1). Both sP-selectin and D-dimer have been previously identified as independent predictors of cancer-associated VTE in the Vienna Cancer and Thrombosis Study (CATS) [39]. P-selectin is an adhesion molecule found in the Weibel–Palade bodies of endothelial cells and α-granules of platelets and is recognized to play a role in thrombosis [40]. When sP-selectin level is elevated above the 75th percentile, it is associated with a 2.6-fold increased risk of VTE compared with patients with sP-selectin levels below the upper quartile [41]. D-dimer is a degradation product of cross-linked fibrin and, when elevated, can indicate the activation of coagulation and fibrinolysis. In a study of 821 patients with newly diagnosed cancer or progression of disease, D-dimer levels were significantly higher in those patients that developed a VTE during the median follow-up period of approximately 17 months [42].

The patient population used to generate the expanded risk model consisted of 819 patients from Vienna CATS enrolled at the time of newly diagnosed cancer or progression of the disease.

Table 1. Expanded model for predicting chemotherapy-associated thrombosis.

Patient characteristics	VTE risk score
Site of cancer	
Very high risk (primary brain, stomach or pancreas)	2
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate or multiple myeloma)	1
Low risk (breast, colorectal or head and neck)	0
Other characteristics	
Platelet count ≥350 × 10^9/l	1
Hemoglobin <100 g/l or use of red blood cell growth factors	1
Leukocyte count >11 × 10^9/l	1
BMI ≥35 kg/m^2	1
sP-selectin ≥53.1 ng/ml	1
D-dimer ≥1.44 μg/ml	1

sP-selectin: Soluble P-selectin; VTE: Venous thromboembolism.
Reproduced with permission from [37].

The median follow-up was much longer in this study than in that of Khorana *et al.* (21.4 months vs 73 days). The authors applied the model developed by Khorana *et al.* to these patients with several modifications based on the differences in cancer type represented in the Vienna CATS patient population. Primary brain cancer, kidney cancer and multiple myeloma cumulatively made up one-fifth of the Vienna CATS patients. Primary brain tumors were added to the very-high-risk category. Kidney cancer and multiple myeloma were added to the high-risk category. Of note, head and neck cancers were not included in this study. The expanded model included one point for each elevated sP-selectin and D-dimer, with cut-off points determined by the previously mentioned studies [41,42]. This model was better able to stratify high-risk patients from low-risk patients with the cumulative probability of VTE of 35% at 6 months with a high-risk score (≥5 points) and 1.0% with a low risk score (0 points) (Table 2). Yet the application of this extended risk-assessment tool is limited by the fact that the sP-selectin assay is not routinely performed in clinical centers and that there is significant variability of D-dimer assays employed.

Table 2. Cumulative probability of venous thromboembolism at 6 months using the expanded risk model before initiation of new therapy.

Risk score	Number of patients	Cumulative probability of VTE at 6 months (%)†
≥5	30	35
4	51	20
3	130	10
2	218	3.5
1	190	4.4
0	200	1.0

†No difference after adjustment for age, sex, chemotherapy, surgery and radiotherapy.
VTE: Venous thromboembolism.

Treatment

Initial treatment

LMWH is the preferred agent for the initial and long-term treatment of VTE in patients with cancer. This recommendation is primarily based on the findings of the CLOT study. This study, which included 676 patients, is the largest randomized clinical trial comparing an LMWH to vitamin K antagonists (VKA). Patients assigned to the VKA (warfarin or acenocoumarol) group initially received dalteparin for 5–7 days and continued with a VKA for 6 months with a target INR of 2.5 (therapeutic range 2.0–3.0). Patients assigned to the LMWH group were given dalteparin 200 IU/kg for the first month and then the dose was reduced to ~150 IU/kg for the remaining 5 months. Over the 6-month follow-up period, 9% of patients in the dalteparin group experienced a symptomatic recurrent VTE compared with 17% of patients in the VKA group, with a relative risk reduction of 52% (hazard ratio [HR]: 0.48; p = 0.002). There was no significant difference between the two groups in terms of bleeding complications or mortality. The need for dalteparin dose reduction after 1 month as well as in the setting of thrombocytopenia and renal insufficiency remains unclear. A total of 90% of patients enrolled had solid tumors in various sites including breast, colorectal, lung, genitourinary, gynecologic, pancreas and brain. A total of 14% of the patients in the dalteparin arm and 16% of the patients in the VKA arm with solid tumors were listed as 'other' for cancer type. The remaining 10% of patients enrolled had hematologic malignancies [43].

Tinzaparin has also been compared with warfarin in a randomized treatment trial of VTE in cancer patients. In a multicenter, open-label, randomized trial, 3-month therapy with tinzaparin was compared with initial unfractionated heparin (UFH) followed by warfarin in 200 cancer patients with VTE. At 12 months, the rate of recurrent VTE in the tinzaparin-treated group was statistically lower than that of the warfarin-treated group (7 vs 16%; p = 0.044; risk ratio: 0.44). However, at the end of the 3 months of active treatment, there was no statistical difference in the VTE recurrence rates between the tinzaparin and warfarin arms suggesting only equivalence during active treatment [44].

Unlike dalteparin, enoxaparin has not been demonstrated to be superior to warfarin. However, the enoxaparin studies were relatively small and may not have been adequately powered to detect a statistical difference. In one study comparing 3-month therapy with enoxaparin sodium (1.5 mg/kg subcutaneously once daily) with warfarin in 146 patients with cancer-associated thrombosis, the enoxaparin arm did not achieve statistical superiority for the combined outcome of major bleeding or recurrent VTE within 3 months (p = 0.09). The rate of recurrent VTE in the enoxaparin group was 2.9% compared with 4.2% in the warfarin group [45]. In another study, which compared 3-month therapy with enoxaparin alone versus initial enoxaparin followed by warfarin in the secondary prevention of VTE in 122 cancer patients, no trends or significance could be determined regarding recurrent VTE between treatment groups because of the low rate of recurrent VTE in the study (four events). The rate of recurrence in the enoxaparin group was 6.5% compared with 10% in warfarin group [46].

A recent meta-analysis compared LMWH and oral VKA in the long-term treatment of cancer-associated thrombosis. It included the five randomized, controlled trials, including four of the above-mentioned studies by Lee *et al.*, Hull *et al.*, Meyer *et al.*, Deitcher *et al.* and one additional study with nadroparin by Lopez-Beret *et al.* [43–48]. In this meta-analysis, LMWH was found to be superior to VKA in the secondary prevention of VTE with relative risk reduction of approximately 50% (relative risk: 0.53; p = 0.007). However, LMWHs have not been shown to reduce the risk of fatal VTE compared with VKA therapy [48].

A recent Cochrane review on initial treatment of VTE with anticoagulants in cancer patients found a statistically significant

mortality reduction with the use of LMWH compared with UFH, but there was insufficient evidence to demonstrate superiority in reducing the recurrence of VTE [49]. It should still be noted that even with the use of LMWH treatment, as many as 10% of cancer patients will have a recurrent or progressive VTE during a 6-month treatment period.

Cost of VTE treatment

The major limitation of LMWH is the associated cost. A Canadian pharmacoeconomic analysis was done based on the CLOT data to measure the economic value of dalteparin for long-term VTE treatment. The overall costs included the costs associated with drug acquisition, monitoring of therapy, adverse events associated with anticoagulation and recurrent VTE. Costs were calculated for the 6-month follow-up period of the original study, with a mean duration of 126.3 days of dalteparin in the experimental group and 8 days in the VKA group. Patients randomized to VKA therapy received treatment for a mean of 116.9 days. The overall costs were lower with VKA than dalteparin, with the cost primarily driven by drug acquisition (Can$2003 vs 4262; $p < 0.001$). When the patient's quality of life was also included in the analysis, dalteparin therapy was considered to be economically acceptable [50].

Duration of VTE treatment

Because cancer is an ongoing risk factor for VTE, the guidelines of the American College of Chest Physicians (ACCP) and ASCO recommend indefinite VTE treatment "as long as the cancer is active" [25,51]. However, the optimal duration of anticoagulation beyond the initial 6-month treatment period is not well studied in cancer patients. Factors such as cost, injection-related discomfort and disposal of the medication may significantly influence patients' willingness to continue with LMWH as opposed to an oral VKA in the long-term treatment of VTE.

Recurrent VTE

ASCO guidelines recommend that patients who develop recurrent VTE despite adequate anticoagulant therapy should be treated with an anticoagulant from a different drug class. Alternatively, according to ASCO guidelines, an inferior vena cava (IVC) filter can be placed, but data supporting the use of IVC filters in cancer patients are lacking [25]. A recent study investigated the use of dose escalation of LMWH in cancer patients with recurrent VTE, suggesting that a higher dose of LMWH may be effective in cases where standard, weight-adjusted doses of LMWH or a VKA have failed [52]. An analysis of 93 patients enrolled in a single-arm trial of tinzaparin for the treatment of cancer-related VTE found a relative risk of 12.2 (95% CI: 1.4–143.8; two-sided $p = 0.0088$) for recurrent thrombosis when patients had a 1-month D-dimer higher than the pretreatment level [53].

Special populations

Renal insufficiency

Treatment of VTE remains a challenge in the setting of renal insufficiency as patients with renal insufficiency have both an increased rate of bleeding and VTE. In the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) study, 10,526 patients with VTE were followed prospectively to examine the effect of renal failure on the incidence of fatal pulmonary embolism (PE) and fatal bleeding within 15 days of diagnosis. Seven hundred and four (6.7%) patients had a creatinine clearance (CrCl) between 30 and 60 ml/min and 588 (5.6%) patients had a CrCl <30 ml/min. Compared with patients with a CrCl >60 ml/min, patients with a CrCl <30 ml/min had a 6.6-fold greater risk of fatal PE (1.0 vs 6.6%) and sixfold greater risk of fatal bleeding (0.2 vs 1.2%). The majority of patients were treated with LMWH (93% of patients with CrCl >60 ml/min and 89% of patients with a CrCl <30 ml/min) [54].

Because LMWH and fondaparinux are excreted renally, these drugs may accumulate, leading to an increased risk of bleeding. However, there is considerable variability in drug accumulation among different LMWHs in patients with renal insufficiency [55–57]. Data suggest that dalteparin may be safe at prophylactic doses in critically ill patients with severe renal failure (CrCl <30 ml/min) [58]. The use of tinzaparin has not been associated with an increased risk of bleeding but has an unexplained increased mortality in older patients [59]. Treatment dose of any LMWH is contraindicated in the setting of severe renal failure and UFH is not well-studied in the long-term treatment of VTE. Therefore, VKA remains the treatment of choice for patients with severe renal insufficiency [51].

Unsuspected PE & PE location

A PE detected on computed tomography (CT) in the absence of clinical suspicion is described as an unsuspected PE (UPE). With the increasingly widespread use of multiple-row detector CT (MDCT), the rate of reported UPEs has increased [60,61]. MDCT improves visualization of pulmonary vasculature in the middle and peripheral lung zones, and has thereby improved the detection of PE. The overall rate of UPE in cancer patients on MDCT scan is reported to be 2.6% with an increased incidence in patients who are hospitalized and with advanced disease [62]. Although this category of PE is often termed 'asymptomatic' or 'incidental', there is evidence to suggest that many of these patients are in fact symptomatic [63]. Furthermore, in a retrospective chart review of 70 cancer patients with UPE, those who reported PE-related symptoms had significantly poorer survival compared with those who were truly asymptomatic [64]. By contrast, in another retrospective review of 51 cancer patients with UPE, there was no difference in 12-month mortality rate between patients with UPE and those with symptomatic PE (52.9 and 53.3%, respectively) [65]. These varying results underscore the importance of prospective studies addressing the implication of UPE in cancer patients in order to guide appropriate treatment.

The management of subsegmental PE (SSPE) is particularly controversial because available data suggest that SSPE may not affect survival, yet the majority of patients are treated. In a retrospective cohort of 94 patients found to have an SSPE on MDCT pulmonary angiography, there was no recurrent VTE, hemorrhage or death reported at 3 months in the 24% of patients who were not treated. Of the 76% who were treated, 97% were

treated with anticoagulant alone or anticoagulant in combination with an IVC filter, resulting in five major bleeding complications, one VTE recurrence and two deaths (neither from PE). This study suggests that the bleeding risk associated with anticoagulation may not outweigh the risk of VTE recurrence given the favorable short-term outcome in patients who were not treated for their SSPE [66].

Importantly, the favorable outcome data of untreated SSPE are derived from studies of the general population, and less is known about the natural history of untreated SSPE in cancer patients. In a retrospective chart review of 70 cancer patients with UPE, there was no significant difference in survival among UPE patients with isolated SSPE and matched controls (HR: 1.04; 95% CI: 0.44–2.39; p = 0.92). However, UPE identified more proximal to the subsegmental arterial branches has a significantly negative impact on survival with an associated HR of 2.28 at 6 months (95% CI: 1.20–4.33; p = 0.011) [67]. Although SSPE may not affect mortality, from a recent survey of 47 physician members of Thrombosis Interest Group of Canada, the presence of metastatic cancer was more likely to prompt physicians to treat SSPE than SSPE in a patient who did not have cancer [68].

Although the ACCP guidelines recommend treating a PE the same regardless of its location or whether it was unsuspected, more prospective research is needed to delineate the clinical relevance of these different types of PE in cancer patients [69].

Brain metastases

Anticoagulation therapy is contraindicated in patients with active intracranial bleeding. Spontaneous intracranial hemorrhage is more common in patients with brain lesions as a result of metastatic disease as compared with patients with primary brain tumor, occurring in 14% of patients with brain metastases versus 0.8% of patients with gliomas [70]. The use of dalteparin for long-term thromboprophylaxis in patients with malignant glioma was shown to increase intracranial bleeding resulting in closure of the PRODIGE trial [71]. Among metastatic brain lesions, thyroid cancer, melanoma, renal cell carcinoma and choriocarcinoma have been associated with high rates of spontaneous hemorrhage [72,73]. However, the majority of CNS metastases arise from lung and breast cancers and have a relatively low risk of intracranial hemorrhage (1–5%) [74,75].

Massive PE

Although the majority of patients with PE are candidates for treatment with anticoagulation therapy, the recommended treatment of patients with massive PE is systemic thrombolysis. The rationale for thrombolytic therapy is that it leads to short-term resolution of emboli and improves hemodynamic instability [69,76,77]. Despite this recommendation, in a study of 108 patients with massive PE, two-thirds of the patients did not receive thrombolysis or embolectomy. Interestingly, of those patients who received thrombolysis, mortality or recurrent PE at 90 days was not reduced [78]. The role of IVC filters, catheter-based interventions and surgical embolectomy in massive PE is yet to be fully established.

Bleeding patient

The only indications for an IVC filter are for those patients who have a contraindication to anticoagulation and those with recurrent VTE despite adequate anticoagulation therapy [45,62]. These recommendations are set forth in the setting of relatively limited evidence. In a study of 400 patients with newly diagnosed proximal DVT comparing anticoagulation with UFH or LMWH alone versus in combination with an IVC filter, the patients treated with IVC had a lower incidence of PE at 12 days but a higher rate of DVT at 2 years, with no difference in mortality [79]. As the patients in the IVC group of this study were also treated with anticoagulation, the benefits of an IVC for patients in whom anticoagulation is contraindicated remains unclear. No randomized trial or prospective cohort study has evaluated IVC filters as monotherapy in patients with DVT without concurrent use of anticoagulation. For this reason, in patients with a DVT in whom an IVC filter has been placed, anticoagulation should be initiated once the bleeding or bleeding risk has resolved [25,69]. Removal of the IVC filter is generally recommended as soon as it is safe to do so in patients with a good prognosis.

Expert commentary & five-year view

There are still a number of important unanswered questions in the long-term management of cancer-related VTE. Whether the Khorana or CATS risk model can be utilized to select cancer patients at high risk for pharmacologic prophylaxis is not known. A clinical trial to assess the efficacy and safety of the Khorana approach is underway [101]. Several studies have shown that primary prophylaxis in ambulatory cancer patients may reduce the rate of VTE without a significant increase in bleeding complications [80–82].

Although LMWHs have proved to be more effective than oral VKA in the prevention of recurrent VTE among cancer patients, their use beyond 6 months has not been studied. Several studies are currently underway investigating the duration of various preparations of LMWH for long-term prevention of recurrent VTE in patients with cancer as well as their efficacy compared with VKA [102–104]. Emerging research suggests that LMWHs may have a variety of antineoplastic effects, and their use may increase survival in cancer patients [83,84].

Unfortunately, patients bear the burden of daily injections, storage and disposal issues, and costs related to the long-term use of LMWH. The new oral anticoagulants may provide a long-awaited alternative for such patients, as well as those presenting with a newly diagnosed VTE, with the added benefit of reliable dosing and few drug interactions. Among the new drugs being investigated are LMWHs, such as bemiparin and semuloparin, and oral factor Xa inhibitors, such as rivaroxaban and apixaban.

Bemiparin is a parenteral LMWH with anti-factor Xa and anti-factor IIa activity. In the CANBESURE trial, prolonged prophylaxis (28 days) with bemiparin was compared with shorter duration prophylaxis (8 days) with bemiparin in patients undergoing

abdominal or pelvic cancer surgery. Prolonged prophylaxis with bemiparin resulted in an 82.4% risk reduction of VTE without significant increase in bleeding (p = 0.010) [85].

Semuloparin is a parenteral ultra-LMWH with anti-factor Xa activity and residual anti-factor IIa activity. In a recent Phase III study of 3212 patients initiating a chemotherapy regimen for locally advanced or metastatic solid tumor, there was a 64% decrease in nonfatal PE or VTE-related death in patients treated with semuloparin compared with placebo without significant increase in bleeding complications [80].

Apixaban and rivaroxaban are both oral direct anti-factor Xa inhibitors. In a recent Phase II study of use of apixaban for VTE prophylaxis in patients with metastatic cancer, apixaban was well tolerated and not associated with increased risk of bleeding [86]. The MAGELLAN trial, which is currently underway, is evaluating extended therapy with oral rivaroxaban in patients hospitalized for acute illness of whom 7.3% have active cancer. Standard-duration enoxaparin (~10 days) will be compared with standard- and extended-duration (~5 weeks) in VTE prophylaxis [87].

LMWH is still the treatment of choice for cancer-related VTE. LMWH preparations are not all alike, however, and some lack evidence for superiority over oral VKAs. We eagerly await the results of ongoing clinical trials aimed at better identifying patient subgroups that merit prophylactic anticoagulation, at determining the optimal duration and type of anticoagulation in this group and at assessing the appropriateness of the new oral anticoagulants among patients with malignancies. Oral factor Xa inhibitors in clinical trials of VTE treatment and prophylaxis enrolled only a limited number of patients with active cancer. They do show promise regarding their efficacy and safety, but need to be more extensively studied in cancer-related VTE-specific trials. However, their cost may be an important limiting factor in their widespread use.

The risk model developed by Khorana *et al.* utilizes easily obtained variables to identify high-risk patients and the results of an ongoing trial are anticipated to determine whether instituting prophylactic antithrombotic therapy in such patients is safe and effective. Also, additional biomarkers such as plasma D-dimer, sP-selectin and/or plasma tissue factor may provide additional criteria to select very high risk cancer patients.

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Key issues

- Venous thromboembolism (VTE) is a common complication among patients with cancer.
- Increased risk of VTE is associated with certain cancer types, advanced disease, surgery, chemotherapy and hospitalization.
- A risk model developed by Khorana *et al.* utilizes easily obtained variables to identify patients at higher risk of VTE.
- Low-molecular-weight heparin is the recommended class of anticoagulants for the treatment of cancer-associated VTE.
- Research is currently underway to determine the optimal duration and type of anticoagulant, and to assess the appropriateness of the new oral anticoagulants among cancer patients.

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• of interest
•• of considerable interest

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