

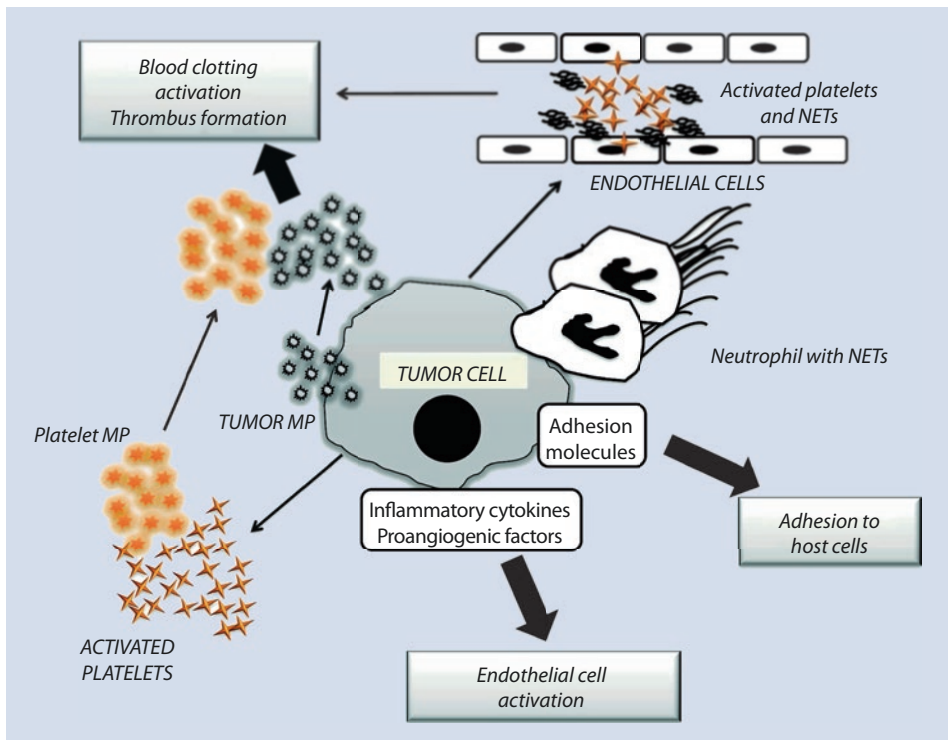
Thromboembolic Disorders as a Consequence of Cancer

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- 4.1 Introduction – 58
- 4.2 Clinical Aspects – 59
- 4.3 Screening for Occult Cancer in Patients with Idiopathic VTE – 59
- 4.4 Primary Thromboprophylaxis and Identification of High-Risk Outpatients – 60
 - 4.4.1 Surgical Prophylaxis – 60
 - 4.4.2 High-Risk Cancer Outpatients Identification for Primary Thromboprophylaxis – 60
 - 4.4.3 Multiple Myeloma – 63
- 4.5 Appropriate Immediate and Long-Term Treatment for Patients with Acute Thromboembolism and the Role of NOACs – 64
 - 4.5.1 Acute Treatment (First 10 Days) – 65
 - 4.5.2 Long-Term (First 3 Months) and Extended Therapy (No Planned Stop Date) – 65
 - 4.5.3 Treatment of Catheter-Related DVT – 66
 - 4.5.4 Vena Cava Filters – 70
- 4.6 Management of Recurrent VTE on Anticoagulation Therapy – 71
- 4.7 Treatment Strategy in Patients with Thrombocytopenia – 71
- References – 72
- Suggested Reading: Society Guidelines – 74

4.1 Introduction

Cancer cells and coagulation system are strictly connected. General prothrombotic mechanisms are related both to the host response to cancer and to the procoagulant activity of cancer cells (■ Fig. 4.1). Host-related factors include the acute-phase reaction, paraprotein production, inflammation, necrosis, and hemodynamic disorders. Malignant cells can activate blood coagulation in several ways. They can produce: procoagulant factors as tissue factor (TF) and cancer procoagulant factor (CP), which are the most powerful procoagulant observed; microparticles (MP); inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1); pro-angiogenic factors as vascular endothelial growth factor (VEGF), which promote both endothelial prothrombotic alterations and angiogenesis. VEGF is an indirect procoagulant that increases microvascular permeability, reprograms gene expression, and promotes the survival of endothelial cells; the resulting increased vascular density plays a key role in the pathophysiology of many cancers. *The same procoagulant factors contribute to tumor progression.* Also platelets, endothelial cells, and neutrophils of host cells are stimulated to express procoagulant activity. *Thus, thromboembolism frequently complicates the course of malignancy and can be the first symptom of cancer [1, 2].*



■ **Fig. 4.1** Cancer-hemostatic system interactions. Tumor cells can activate the hemostatic system in multiple ways. Tumor cells release procoagulant activities, and microparticles (MP), by which the coagulation cascade is activated. Tumor cells also activate the host hemostatic cells (endothelial cells, leukocytes, and platelets), by either release of soluble factors or direct adhesion contact, thus eliciting the expression of a procoagulant phenotype of these cells. In addition, the neutrophils can release neutrophil extracellular trap (NETs), and the adhesion of a large quantity of NETs to the vasculature may initiate thrombosis by providing a scaffold for platelet adhesion, activation, and thrombin generation. Reproduced with permission from [1]

4.2 Clinical Aspects

- The more common events are venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE is the second-leading cause of death in patients with malignancy [3].
- The arterial thrombotic events (ATE) in cancer are common after treatment with anti-angiogenic drugs, cisplatin, and hormonal therapies [4, 5].
- The cardiovascular risk factors associated with the hypercoagulability of cancer contribute to the precipitating of thrombotic events. VTE incidence is significantly different ($P < 0.0001$) for the different types of cancer, with the higher rate observed in patients with pancreatic cancer (19.2%) and the lowest in patients with bladder cancer (8.2%) [6]. Although DVT is more common in patients with pancreatic cancer (12.6%), the PE is more common in lung (3.6%) and gastric cancers (3.3%).
- VTE is also associated with recurrent VTE as well as bleeding, both at significantly higher rates than seen in non-cancer patients [7].
- Systemic chemotherapy increases the risk of VTE sixfold–sevenfold, and the rise in cancer-associated VTE over recent decades may have been caused in part by the introduction of therapies with direct effects on the vascular endothelium [6].
- Clinically apparent VTE occurs in as many as 10% of patients with cancer, but autopsic studies have described higher rates of thrombosis in some subgroups: for example the patients who died of pancreatic cancer, [1, 7–9].
- VTE is associated with a threefold increase in hospitalizations and an increased health-care resource utilization and costs. It is vital to adopt appropriate strategies for prevention and treatment of venous thromboembolism in order to reduce its impact in patients with cancer and health care system. [10].

4.3 Screening for Occult Cancer in Patients with Idiopathic VTE

An “idiopathic” VTE may be the first clinical sign of a tumor; up to 10% of patients with unprovoked VTE receive a cancer diagnosis within the first year subsequent to the event, and more than 60% of occult cancers are diagnosed shortly after the diagnosis of idiopathic VTE [2, 11]. The utility of using an extensive screening for the purpose of early identification of an occult neoplasm is controversial. In the absence of specific guidelines, clinical practice is very variable and differs depending on the prevailing beliefs of the individual centers. A recently published study compared a limited occult cancer screening (basic blood testing, chest radiography, age screening for breast, cervical, and prostate cancer) to limited occult-cancer screening in combination with computed tomography (CT) of the abdomen and pelvis. There was no significant difference between the two study groups in the mean time to a cancer diagnosis (4.2 months in the limited-screening group and 4.0 months in the limited-screening-plus-CT group, $P = 0.88$) or in cancer-related mortality (1.4 and 0.9%, $P = 0.75$) at 1-year follow-up [12].

- **For patients with a first episode of unprovoked VTE, a limited testing for cancer, including a history and physical examination, complete blood count, serum chemistries, liver function tests and urinalysis, routine age-appropriate cancer screening, and chest radiography, is actually suggested [13].**

4.4 Primary Thromboprophylaxis and Identification of High-Risk Outpatients

4.4.1 Surgical Prophylaxis

- *After abdominal or pelvic surgery for cancer, thromboprophylaxis with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) reduces the risk of deep vein thrombosis by about 15%.*
- *UFH versus LMWH.*
 - *In the ENOXACAN study (designed to compare the efficacy and safety of LMWH enoxaparin 40 mg/day versus UFH at low doses, in the prophylaxis in cancer abdominal or pelvic surgery), the incidence of DVT was 18.2% in patients with UFH and 14.7% in the group with enoxaparin [14].*
 - *a meta-analysis that included 16 clinical trials with 12,890 patients with cancer found no major differences between the perioperative thromboprophylaxis with LMWH compared with UFH in their effects on mortality, VTE, and bleeding in patients with cancer.*
 - *The advantage of single daily dosing, the most favorable pharmacological profile, and the lower association with heparin-induced thrombocytopenia make the most used LMWH compared with UFH [15, 16].*
- *The benefit of a longer duration of postoperative anticoagulation than typically used for individuals without cancer was shown in three separate trials that randomized patients undergoing major cancer surgery to 1 week versus 4 weeks of a LMWH.*
 - *These trials all showed a significant reduction in the incidence of VTE after 4 weeks of anticoagulation compared with 1 week (5 versus 12%, 7 versus 16%, and 13 versus 10%) [17–19].*
 - *None of the trials showed increased bleeding in the prolonged anticoagulation group. Although it remains to be confirmed that extended thromboprophylaxis improves survival or is cost-effective after surgery for cancer, extended prophylaxis up to 4 weeks after surgery for cancer is recommended by consensus guidelines.*
- *As regards the laparoscopic surgery, a significant difference in the incidence of postoperative VTE was not observed when compared to traditional open surgery [20].*

4.4.2 High-Risk Cancer Outpatients Identification for Primary Thromboprophylaxis

A recent systematic review estimates the overall risk of VTE to be 13 per 1000 person-years (95% CI, 7–23). The risk of VTE was 68 per 1000 person-years (95% CI, 48 to 96) in patients considered at high risk for metastatic disease or high-risk treatments. The highest risk is in patients with brain cancer (200 per 1000 personyears; 95% CI, 162–247).

Table 4.1 Risk factors for thromboembolism

<p><i>General</i></p> <ul style="list-style-type: none"> Older age Female gender African or Afroamerican ancestry Previous VTE Hypertension Infections Limited mobility 	<p><i>Treatment related</i></p> <ul style="list-style-type: none"> Hospitalization Surgery Antiangiogenic agents Hormonal therapy Erythropoiesis-stimulating agents Blood transfusions Central venous lines
<p><i>Cancer related</i></p> <ul style="list-style-type: none"> Site (brain, pancreas, kidney, stomach, lung, bladder, gynecologic, hematologic malignancies) Advanced stage Short time after initial diagnosis 	<p><i>Biomarkers</i></p> <ul style="list-style-type: none"> Platelet count ($\geq 350,000/\mu\text{L}$) Leukocyte count ($\geq 11,000/\mu\text{L}$) D-dimer TF P selectin TFMP Hyperlipidemia

Modified from Falanga and from ASCO guidelines [1, 22]

► An appropriate risk stratification of patients is therefore crucial to highlight which patients should receive prophylaxis [21].

Clinical risk factors, biomarkers, or combinations of the two can be used to estimate VTE risk.

- *Clinical risk factors* include tumor type, location, stage, and time since diagnosis influence VTE risk, along with patient comorbidities and therapeutic interventions (Table 4.1).
 - Factors related to treatment are: surgery, chemotherapy, hormonal therapy, anti-angiogenic agents (thalidomide, lenalidomide, bevacizumab), central venous catheters, erythropoiesis-stimulating agents (ESAs), blood transfusions.
 - VTE risk *after surgery* is 2 times higher in patients with known cancer than in the general population; 1/3 of events occur after discharge, and mortality is more than six times higher in patients with VTE compared to those without VTE (8 versus 1.2%) [23].
- *Individuals with cancer should be considered high risk for development of postoperative VTE. This increased risk is reflected in the Caprini score for VTE in surgical patients, which assigns two points for the presence of malignancy.*
 - *Chemotherapy* with cisplatin and fluorouracil may induce thrombogenic effects through multiple mechanisms that include the secretion by the tumor cells of pro-angiogenic and immunomodulatory cytokines, increase of TF on endothelial cells, direct toxicity on the endothelium, and reduced synthesis of C protein.
 - *Erythropoiesis-stimulating agents (ESA)* reduce the need for transfusions and improve quality of life but cause an increased incidence of VTE and mortality [23].

Table 4.2 Predictive model for VTE. Points for the risk model are based on the regression coefficients obtained from the final model and divided the population into 3 risk categories based on the score from the risk model: low (score 0), intermediate (score 1-2), and high (score 3; not present)

Patients Characteristic	Score
Site of cancer	2
Stomach, pancreas (very high risk)	1
Lung, lymphoma, gynecologic, bladder, testicular	1
Prechemotherapy platelet count $\geq 350,000/\text{mm}^3$	1
Hemoglobin level $< 10 \text{ g/dL}$ or use of red cell growth factors	1
Pre chemotherapy leukocyte count $> 11,000/\text{mm}^3$	1
Body mass index (BMI) $\geq 35 \text{ Kg/m}^2$	1
High-risk score ≥ 3 ; intermediate 1–2; low 0	

Modified from Khorana et al. [34]

- The advent of novel “targeted” anticancer therapies has not reduced the risk of VTE. Indeed, drugs targeting angiogenesis such as bevacizumab, sunitinib, sorafenib, and the multi-targeted tyrosine kinase inhibitor ponatinib have been associated with arterial thromboembolism.
- Immunomodulatory agents such as thalidomide and lenalidomide have been associated with very high rates of VTE, and anti-epidermal growth factor antibodies such as cetuximab and panitumumab have also recently been associated with VTE [24–26].
- A particularly high risk has been reported in patients receiving chemotherapy in combination with antiangiogenic agents. The highest incidence of VTE in myeloma occurs during treatment with thalidomide associated with anthracyclines (12–28%), thalidomide with dexamethasone at high doses (17–26%), lenalidomide, and high dose of dexamethasone (18–26%) [27–30].
 - A variety of biomarkers have also been associated with VTE in malignancy. These include platelet count $\geq 350,000$ before chemotherapy, white blood cell count $> 11,000$ before chemotherapy, hemoglobin value $< 10 \text{ g/dL}$, elevated tissue factor expression on the surface of cancer cells, high activity of circulating tissue factor, elevated D-dimer, elevated soluble P-selectin, thrombin generation, and levels of TF bearing microparticles (TFMP) [31–33].
 - A validated model to guide clinical decisions on thromboprophylaxis in patients treated with chemotherapy has been developed by Khorana. The Khorana score is calculated by assigning points for clinical parameters available for patients (i.e., site of primary tumor, hematologic parameters, and body mass index) [34] (Table 4.2).
 - This risk score was originally derived from a development cohort of 2701 patients and then validated in an independent cohort of 1365 patients, stratified into three

risk groups to predict the development of VTE. The cumulative incidence of VTE at 2.5 months ranged from 0.3 to 6.7 % in patients with the fewest and most risk factors, respectively.

Subsequently, the score was externally validated prospectively, and modified version of the score was used in an observational cohort study: the *Vienna Cancer and Thrombosis Study (CATS)*. The modified score included:

- Additional high-risk tumor types (brain, myeloma, kidney).
- Two additional laboratory values: soluble P-selectin and D-dimer levels.
- In a retrospective analysis, the cumulative incidence rates of VTE at 6 months were 1 % for the lowest risk group (0 points) and 35 % for the highest risk group (≥ 5 points) [35].

Recently, the same working group has explored the utility of soluble plasma VEGF-A (sVEGF) as a biomarker for the prediction of VTE in patients with cancer, and elevated sVEGF is proved to be associated with an increased risk of VTE in patients with cancer [36].

In the *PROTECHT score*, the inclusion of chemotherapy with platinum (carboplatin, cisplatin) or gemcitabine over the five variables identified high-risk cancer patients in a post hoc analysis of the *PROTECHT* study. Patients with higher absolute risk of VTE would derive the most benefit as demonstrated by the analysis of subgroups of two largest randomized trials.. Rates of VTE in high-risk patients enrolled in *PROTECHT* were 11.1 % in the placebo arm and 4.5 % in the nadroparin arm (NNT = 15 versus 77 for low and intermediate-risk patients) [37].

In the subgroup analysis of *SAVE-ONCO*, rates of VTE in patients with Khorana risk score ≥ 3 were 5.4 % in the placebo arm and 1.5 % in the semuloparin arm (NNT = 25 for high-risk patients to 333 for low-risk patients) [38].

Anticoagulant prophylaxis has been shown to reduce the risk of VTE in medical patients, but none of the trials reported the rates of symptomatic venous thromboembolic events or major bleeding episodes according to cancer status; recommendations are therefore made based upon extrapolation of data from randomized trials that included only a small minority of cancer patients [39].

4.4.3 Multiple Myeloma

VTE incidence is about 5 % in myeloma patients treated with conventional chemotherapy. The anti-angiogenic agents for the treatment of multiple myeloma, such as thalidomide and lenalidomide, are known to activate endothelial cells and platelets, and to damage the vascular endothelium, increasing the thrombotic risk. VTE incidence is particularly high when thalidomide or lenalidomide is combined with high-dose dexamethasone (480 mg/month), with doxorubicin or with polichemotherapy. For patients with multiple myeloma, a risk assessment model has been proposed from the Myeloma Working Group. It takes into account individual risk factors, factors linked to the disease and therapy [27].

Special Recommendations

- Aspirin is recommended for patients with 0–1 risk factors.
- Enoxaparin 40 mg per day or full-dose warfarin (target INR 2–3) are indicated both for patients with two or more individual risk factors related to myeloma, both for patients treated with thalidomide/lenalidomide associated with high-dose dexamethasone and/or doxorubicin.
- A randomized study compared the effectiveness of low dose aspirin, 1.5 mg/day dose warfarin, and enoxaparin 40 mg in patients with newly diagnosed myeloma treated with thalidomide-based regimens, cortisone and melphalan or bortezomib. Similar efficacy of therapeutic regimens in reducing VTE in elderly patients was observed; however, enoxaparin showed greater efficacy compared to warfarin in reducing major thromboembolic events, acute cardiovascular events, and sudden deaths [40].
- Another study compared low-dose aspirin with enoxaparin 40 mg in patients treated with lenalidomide.
 - The incidence of VTE was 2.27 % in the aspirin group and 1.2% in the LMWH group, suggesting that aspirin is an effective therapeutic alternative for patients at “standard” risk [41].
- It was also noted that the treatment with bortezomib reduces the 2% risk of VTE for an antithrombotic effect due to the synthesis of nitric oxide which would result in a reduced platelet activation [42].
- All patients with malignancies undergoing major surgery should be considered for both pharmacological thromboprophylaxis with UFH or with LMWH, unless contraindicated due to active bleeding or high risk of bleeding.
- Once daily LMWH, UFH three times a day or fondaparinux is recommended to prevent postoperative VTE in patients with cancer.
- Pharmacological prophylaxis should be started 12–2 h before surgery and continued for at least 7–10 days. Use of fondaparinux must be made 6 h after surgery.
- The extended prophylaxis for 4 weeks in patients with a high risk of VTE (pelvic and abdominal surgery) and low bleeding risk for patients undergoing abdominal or pelvic surgery for cancer with high-risk features such as reduced mobility, obesity, history of VTE, or other risk factors is recommended.
- The use of LMWH for the prevention of VTE in cancer patients undergoing laparoscopic surgery is recommended as for laparotomy.
- Mechanical methods are used in association with drug therapy in high-risk patients but are not recommended as monotherapy except when pharmacological prophylaxis is contraindicated for active bleeding or high risk of bleeding.

4.5 Appropriate Immediate and Long-Term Treatment for Patients with Acute Thromboembolism and the Role of NOACs

The goal of therapy is to resolve the acute episode and to prevent recurrence, extension, and embolism while minimizing the risk of bleeding. However, treatment of VTE in cancer is complicated due to higher rates of recurrent VTE as well as a higher risk of bleeding with anticoagulation treatment.

4.5.1 Acute Treatment (First 10 Days)

- The therapeutic options for VTE in the acute phase include UFH, LMWH, and Fondaparinux.
 - Few studies have directly compared the anticoagulant therapy for the initial treatment of VTE in cancer patients. In a meta-analysis of 16 randomized controlled trials in cancer patients treated with anticoagulants for VTE, LMWH compared to UFH was associated with a reduction in mortality at 3 months (RR 0.71; 95 % CI 0.52, 0.98) without an increased risk of bleeding [43].
 - LMWH offers other advantages over UFH: cost, ease of dosing and a lower risk of heparin-induced heparin (HIT).
- **There are no studies in the literature of direct comparison between fondaparinux and LMWH for the initial treatment of VTE.**
 - UFH can be used in patients with severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) because the liver is a main site of heparin biotransformation. Other advantages of UFH are the short half-life and the reversibility of effect with protamine sulfate.
 - The initial dose of UFH for VTE treatment is based on weight, with the recommended dose of 80 units/kg bolus followed by 18 units/kg/h infusion.
 - UFH is contraindicated in patients with HIT, and in this situation fondaparinux or a thrombin inhibitor represents a better alternative.
 - Fondaparinux is not the first choice in patients with cancer because of the long half-life, the absence of an effective antidote, and the renal clearance of 100 %.
 - Analysis of Matisse-DVT trial subgroup showed higher rates of recurrent VTE in the fondaparinux group than in the enoxaparin group: 12.7 % compared with 5.4 % with no differences in mortality and bleeding [44].

Currently, the use of LMWH for the initial treatment of VTE patients with cancer is recommended as treatment of choice.

4.5.2 Long-Term (First 3 Months) and Extended Therapy (No Planned Stop Date)

- The minimum duration of anticoagulant therapy for VTE is usually 3 months; this period of treatment is referred to as “long-term therapy.” For long-term therapy, the possible options are vitamin K antagonists (VKA), LMWH, Fondaparinux, and new oral anticoagulants (NOACs) ad dabigatran, rivaroxaban, apixaban.
- A meta-analysis of seven randomized clinical trials involving cancer patients with VTE showed a significant reduction of recurrent VTE in patients treated with LMWH compared with those treated with VKA [45].
- LMWH are preferred to VKA therapy in patients with cancer for several reasons: there is a substantial rate of recurrent VTE in patients with VTE and cancer who are treated with VKA; benefits of LMWH compared to VKA therapy are greater in patients with metastatic disease treated with aggressive chemotherapy [46]; it is often harder to keep patients with cancer who are on VKA in the therapeutic range; LMWH is reliable in patients who have difficulty with oral therapy; and LMWH is easier to withhold or adjust than VKA if invasive interventions are required or thrombocytopenia develops.

- In the *CLOT trial*, the efficacy and safety of immediate dalteparin (200 units/kg daily for 5–7 days) followed by chronic (6 months) therapy with an oral coumarin derivative are compared versus chronic dalteparin therapy (200 units/kg daily for 1 month followed by 150 units/kg for months 2–6) in patients with cancer (most of patients had metastatic disease) after diagnosis of acute proximal DVT, PE, or both. Full dose dalteparin was given for 1 month followed by a reduced dose (75–80 %) for 2–6 months.
- Prolonged treatment with LMWH for 6 months reduced thromboembolic recurrence from 17 to 9% ($P=0.0017$), compared to standard therapy without increasing the risk of bleeding [46].
- The *CATCH study* evaluated the efficacy and safety of *tinzaparin* in patients with active cancer and symptomatic VTE. The patients were randomized to receive tinzaparin 175 IU/kg once a day for 6 months or initial tinzaparin 175 IU/kg once a day for 5–10 days followed by warfarin for 6 months.
- Tinzaparin significantly reduced the risk of recurrent symptomatic DVT, nonfatal and clinically relevant bleeding [47].
- *Fondaparinux* seems to have a similar safety and efficacy profile as LMWH [48].
- Studies focused on the use of NOAC in cancer patients are still lacking. Preliminary results of the subgroup analyses and meta-analysis of randomized clinical trials suggest that they have efficacy and safety comparable to anticoagulation with VKA and could represent an alternative for oral anticoagulant therapy.
- A meta-analysis of six RCTs assessed the efficacy and safety of NOACs in patients with cancer-associated VTE. NOACs were shown to be as effective (OR 0.63, 95 % CI 0.37–1.10) and as safe (OR 0.77, 95 % CI 0.41–1.44) as warfarin [49]. The risk reduction for recurrent VTE with the NOACs compared to LMWH has not been assessed but, based on indirect comparisons, LMWH may be more effective than the NOACs in patients with VTE and cancer.
- However, the small number of patients with cancer (5–8 %) enrolled in each study and the use of warfarin or placebo rather than LMWH in the control do not support yet their use for this population [22, 49–61].
- Furthermore, there are interactions with some chemotherapeutic agents [49].
- NOACs have not been compared with VKA in a broad spectrum of patients with VTE and cancer, and indirect comparisons have not shown convincingly different outcomes with different NOACs (■ Table 4.3).
- A preference for one NOAC over another or for either a NOAC or VKA in patients with cancer cannot presently be expressed.

See ■ Tables 4.3 and 4.4 for further details on indications and dose of anticoagulant as prophylaxis and therapy, according to different guidelines.

4.5.3 Treatment of Catheter-Related DVT

Permanent central venous catheters (CVC) are usually regularly washed with heparin to maintain their patency. However, symptomatic catheter-related venous thrombosis may occur in 4–8 % of patients. Clinical symptoms include edema, pain, and erythema

■ **Table 4.3** Key points of most recent guidelines

ACCP 2016	ASCO 2015	NCNN 2015	BSH 2015
Thromboprophylaxis			
	<p>Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization.</p> <p>Routine thromboprophylaxis may be considered for selected high-risk patients. Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low-molecular weight heparin (LMWH) or low-dose aspirin to prevent VTE. Extending postoperative prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features.</p>	<p>Dose adjustments are required for obese patients receiving prophylaxis with dalteparin, enoxaparin, UFH, or fondaparinux.</p> <p>Prophylactic anticoagulation therapy should be considered for all inpatients with cancer without contraindication to such therapy. Following hospital discharge, it is recommended that cancer patients in a high-risk setting for VTE continue to receive VTE prophylaxis, with the duration of anticoagulation determined by the clinical situation. Patients with multiple myeloma who are receiving lenalidomide- or thalidomide-based combination regimens associated with a high thrombotic risk or patients with two or more individual or disease-related risk factors should receive prophylaxis strategy with either LMWH (e.g., enoxaparin 40 mg daily) or dose adjusted warfarin (INR 2–3)</p> <p>Patients with cancer at high risk for VTE (based on Khorana risk assessment score 3 or higher) could be considered for outpatient VTE prophylaxis on an individual basis.</p>	<p>Patients undergoing abdominal and pelvic surgery for cancer should be considered for extended thromboprophylaxis (2B). Thromboprophylaxis should be considered for high-risk outpatients (2B). Patients with active or recent cancer admitted to hospital should receive thromboprophylaxis unless contraindicated (2C). Patients with myeloma receiving thalidomide or lenalidomide should be risk-assessed for VTE and offered thromboprophylaxis unless there is a contraindication (1A). A platelet count of $<50 \times 10^9/L$ is a relative contraindication to pharmacological prophylaxis.</p>

(continued)

■ **Table 4.3** (continued)

ACCP 2016	ASCO 2015	NCNN 2015	BSH 2015
Treatment			
<p>LMWH are the preferred long-term treatment for VTE and cancer</p> <p>Extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), is recommended in patients who do not have high bleeding risk and suggested in patients who have high bleeding risk (Grade 2B)</p> <p>A reassessment at periodic intervals is recommended in all patients who receive extended anticoagulant therapy.</p> <p>In patients with VTE and cancer who are not treated with LMWH, a NOAC or VKA could both be considered. Moreover, there isn't any convincing evidence that NOAC is superior to another.</p>	<p>LMWH are recommended for the initial 5–10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months</p> <p>Use of novel oral anticoagulants is not currently recommended for patient with malignancy and VTE</p>	<p>LMWHs are preferred for acute management of VTE in cancer patients because they do not require hospitalization or monitoring and are the preferred option for long-term therapy</p> <p>The use of LMWHs as chronic anticoagulation therapy is supported in patients with metastatic disease who are diagnosed with acute VTE</p> <p>Use of novel oral anticoagulants for acute and extended chronic treatment of VTE in patients with cancer remains to be investigated in future prospective trials</p>	<p>Initial treatment should be with LMWH for 6 months, if tolerated (1A).</p> <p>In the presence of active malignancy, anticoagulation should be continued (2B).</p> <p>When the platelet count is $<50 \times 10^9/L$, platelet support should be given to elevate the count to $>50 \times 10^9/L$ to allow full dose anticoagulation, especially in the immediate period following thrombosis development (2D).</p> <p>Patients with platelet counts between 25 and $50 \times 10^9/L$ should have frequent assessment to allow decisions on LMWH to be made (2D).</p> <p>If the platelet count remains $<25 \times 10^9/L$, full anticoagulation should be avoided (1D).</p> <p>Warfarin and other oral anticoagulants are acceptable alternatives if LMWH is impractical and anticoagulation is indicated (1A).</p>

of the affected limb; most of the CVC are inserted in the superior vena cava: thus, there may be swelling of the neck, supraclavicular area, or face. The thrombosis can develop acutely or over a more prolonged period of time. In case of thrombosis, the choice is influenced by the need of maintaining the device for further antineoplastic treatments of the patient [61, 62].

- The removal is recommended if the device is no longer required or when patency cannot be restored by thrombolysis and/or anticoagulation; there are contraindications to anticoagulation (active bleeding, platelet count $<50,000/\mu L$, or recent central nervous system bleeding or surgery), if the catheter is infected or dysfunctional.

Table 4.4 Recommended dosing regimens for cancer associated VTE

	Standard dosing	Obese patients (≥ 40 Kg/m ²)
Prophylaxis		
Outpatients		
UFH	5000 UI SC ^b once every 8–12 h	7500 UI every 8 h
Dalteparin Nadroparin Enoxaparin Fondaparinux Tinzaparin	5000 UI SC OD ^c 3800 UI SC OD 4000 UI SC OD 2.5 mg SC OD 4500UI SC OD or 75 units/kg OD	7500 UI SC OD 4000 UI SC OD 5 mg SC every 12 h
Aspirin	81–325 mg (low risk myeloma)	
Inpatients		
Medical patients		
UFH Dalteparin Enoxaparin Fondaparinux	5000 UI SC every 8–12 h 5000 UI SC OD 4000 UI SC OD 2.5 mg SC OD	
Surgical patients		
UFH Dalteparin Enoxaparin Fondaparinux	5000 UI 2–4 h preoperatively and 5000 UI OD postoperatively 2500 UI 2–4 h preoperatively and 5000 UI OD postoperatively 4000 UI 10–12 h preoperatively and 4000 UI OD postoperatively 2.5 mg OD beginning 6–8 h postoperatively	
Warfarin	INR target 2–3	
Treatment		
<i>Initial</i>		
UFH ^a Dalteparin Tinzaparin Enoxaparin Fondaparinux	80 UI/kg IV bolus, then 18 U/kg/h IV; adjust dose based on a PTT 100 UI/kg once every 12 h; 200 U/kg OD 1 mg/kg once every 12 h; 1.5 mg/kg OD 1 mg/kg once every 12 h; 1.5 mg/kg OD <50 kg, 5.0 mg OD; 50–100 kg, 7.5 mg OD; 100 kg 10 mg OD	
<i>Long term</i>		
Dalteparin Enoxaparin Tinzaparin	200 UI/kg OD for 1 month, then 150 U/kg OD 1.5 mg/kg OD; 1 mg/kg once every 12 h 175 UI/Kg OD	
Warfarin	INR target 2–3	

According to ASCO and NCNN guidelines [22, 58, 59]

^aUnfractionated Heparin

^bSubcutaneously

^cOnce a day

- Before removing the device, a short time (5–7 days) of anticoagulant therapy is recommended to reduce the risk of embolization. Therefore evaluation of the likelihood and consequences of embolization according to the size and location of the thrombus should be carried out.
- Patients with cancer who have had their CVCs removed and then replaced without anticoagulation often experience recurrent thrombosis.
- Anticoagulant therapy with LMWH is recommended if the catheter must remain in situ for a period of at least 3 months up to 6 months [62].
- Thrombolytic therapy is justified in cases of thrombosis of the superior vena cava with caval syndrome poorly tolerated or complete occlusion of the CVC. Instillation of 2 mg of t-PA or Urokinase 10,000 IU infused in each catheter lumen for 4 h once a week may restore catheter patency.
- In case of symptomatic CVC thrombosis, anticoagulant treatment is recommended for a minimum of 3 months.
- In this setting, LMWHs are suggested. Oral VKA can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting.
- The CVC can be kept in place if it is functional, well-positioned, and noninfected with good resolution of symptoms under close surveillance.

4.5.4 Vena Cava Filters

- The implantation of inferior vena cava (IVC) filters should be restricted to patients with VTE and/or PE and contraindications to anticoagulation [63].
 - Active bleeding.
 - High risk of bleeding.
 - Undergoing surgery at high risk of bleeding (as major abdominal surgery).
- Their use in patients with recurrent thrombotic events despite anticoagulant therapy does not appear logical because the filters do not treat the condition of thrombosis, and the presence of an intravascular foreign body is likely to promote the formation of a thrombus proximal or distal to the thrombus filter.
 - IVC thrombotic occlusion is the presence of an occluding thrombus in the IVC after filter insertion can be symptomatic or asymptomatic and remains a serious complication of IVC filtration. The reported incidence ranges from 2 to 30 %.
 - Renal failure secondary to renal vein thrombosis has been reported after suprarenal filter placement. Suprarenal filters should be avoided in patients with a single functional kidney, renal insufficiency, or previous renal vein thrombosis.
- The possible complications of inferior vena cava filters are [64]:
 - Penetration of the vein wall by a filter strut or anchor device with transmural incorporation, with secondary lesion to the neighbouring structures.
 - Filter embolization, defined as post-deployment movement of the filter or its components to a distant anatomic site (heart and pulmonary tree).
 - Filter fracture (i.e., breakage or separation); the reported incidence of filter fracture is as high as 2–10 %.
- *Retrievable devices should be used, and possibly be removed, re-starting the anticoagulant therapy, as soon as possible [63, 64].*

Special Recommendations

- Brain tumor in itself is not a contraindication to anticoagulation therapy in VTE. For the treatment of VTE in patients with brain tumor, it is preferable to use LMWH for 6 months in all patients except those with tumors that have a high rate of intracranial hemorrhage (metastases from melanoma, choriocarcinoma, thyroid carcinoma, and renal cell carcinoma).
- There is no evidence to recommend LMWH or UFH over another in elderly patients with active malignancy. Tinzaparin might have a favorable biologic profile using therapeutic dosing in the setting of renal insufficiency.
- In patients with renal insufficiency and $\text{Ccr} < 30 \text{ mL/min}$, enoxaparin might have a less favorable biologic and the dosage should be reduced a 1 mg/kg sc every 24 h or factor Xa will be monitored UFH, tinzaparin and dalteparin are preferred as agents.
- In cancer patients who are pregnant, standard prophylaxis should be implemented.
- Heparin-induced thrombocytopenia (HIT), due to the formation of antibodies against a complex platelet factor 4 (PF4)/heparin, is a consumptive thrombocytopenia associated with a serious pro-thrombotic state. The treatment of HIT is based on the use of direct thrombin inhibitors, such as lepirudin (0.08 mg/kg/h, to be halved in case of kidney failure), argatroban, and bivalirudin. Fondaparinux may be an alternative, but its use is not consolidated and is considered off-label.

4.6 Management of Recurrent VTE on Anticoagulation Therapy [55, 63–67]

- In patients with thrombosis occurring during treatment with oral anticoagulant, a relapse with INR not in the therapeutic range requires a dose adjustment in order to obtain INR in the range between 2 and 3.
- For recurrent VTE on a non-LMWH anticoagulant, LMWHs are suggested.
- If recurrence occurs in the course of LMWH at subtherapeutic doses (75–80%), the re-administration of the LMWH at full dose may be effective in more than 90% of patients and for recurrent VTE on full dose of LMWH; the dose may be increased by about 25%.
- If the patient is taking medications that increase the risk of thrombosis such as estrogens or chemotherapy, these treatments should be possibly withdrawn.

4.7 Treatment Strategy in Patients with Thrombocytopenia

- In patients with thrombocytopenia, full doses of anticoagulation can be used for VTE treatment if the platelet count is $\geq 50,000$, and there is no evidence of bleeding.
- For patients with a platelet count of 20,000–50,000, a 50% of full dose must be employed.
- Stop anticoagulants for a count $< 20,000$ always adapting the decision to the individual case.
- If severe cancer or chemotherapy-induced thrombocytopenia is present, platelet transfusions may be used to allow anticoagulation; an experience of few cases reported in the literature suggests that the use of prophylactic doses of LMWH can be tolerated in patients with platelet counts $\leq 20 \times 10^9/\text{L}$ with associated resolution of thrombotic symptoms [67].

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