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IM - REVIEW

Position paper of the Italian Society of Internal Medicine (SIMI) on prophylaxis and treatment of venous thromboembolism in patients with cancer

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Abstract
Cancer patients are at high risk of developing thrombotic events, including venous thromboembolism (VTE) [deep venous thrombosis (DVT) and pulmonary embolism (PE)], and arterial thrombosis. DVT and PE represent the second leading cause of death in cancer patients; moreover, the development of thromboembolic events in cancer patients is linked to a greater need of hospitalization and frequency of side effects during treatment, in particular bleeding, and to an increased risk of recurrence during and following antithrombotic therapy. The thromboembolic risk may be different in different subgroups of cancer population, being highest in patients with metastatic disease, patients with pancreas, stomach, kidney or primary brain cancer, or during therapeutic interventions or surgery. This document focuses on several relevant topics including the epidemiology and pathogenesis of cancer-associated VTE, the current and future strategies of primary prevention and anticoagulant treatment, and the management of bleeding complications. The main literature data are discussed in detail, including, when available, evidence from randomized clinical trials and meta-analyses, international guidelines statements, the results of recently published trials comparing direct oral anticoagulants to low molecular weight heparin, and the design and aims of ongoing trials on prevention/treatment of cancer-associated VTE.

Keywords Venous thromboembolism · Cancer · Anticoagulant therapy · Bleeding

Introduction

Cancer patients are at high risk of developing thrombotic events, including venous thromboembolism (VTE) [deep venous thrombosis (DVT), pulmonary embolism (PE)], and arterial thrombosis. These complications contribute to the considerable morbidity and mortality of cancer, considering that VTE is the second leading cause of death in these patients [1–4], second only to cancer itself, and may precede or coincide with its diagnosis. These patients are at an increased risk of VTE recurrence or bleeding during anticoagulant therapy. Moreover, the diagnosis and management of thromboembolic events often interrupt or delay essential cancer treatments [5]. Incidental VTE, including splanchnic thrombotic events, further contributes to the thromboembolic burden in cancer patients. For these reasons, the management of VTE events in cancer patients is challenging and often suboptimal.

Purpose The aim of this statement is to provide Italian internists with the opinion of some experts of Italian Society of Internal Medicine (SIMI) on available data, sometimes still scarce or controversial, and with recent emerging evidence, concerning the prophylaxis and treatment of VTE in patients with cancer, and the use of antithrombotic drugs in this setting.

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This paper is also devoted to illustrating how the introduction of direct oral anticoagulants (DOACs) has created a new opportunity for the treatment of these patients by also providing the possibility of rapid hospital management with low mortality risk and new perspectives for prevention of relapses.

Vte in patients with cancer: epidemiology and mechanisms

Epidemiology

The incidence of VTE in patients with cancer is about four to seven times higher than in healthy subjects [6, 7], and has been increasing over recent years thanks to improved patient survival, more aggressive cancer treatments, and a better awareness of cancer-associated thrombosis [8]. It is estimated that about 15% of cancer patients will develop VTE, and that about 20% of patients with VTE have an unknown neoplasm at the time of diagnosis [8]. DVT and its complication, PE, represent the second leading cause of death in cancer patients; moreover, in this setting, the development of VTE is linked to an increased risk of hospitalization and frequency of side effects during anticoagulant treatment, in particular bleeding, and to an increased risk of recurrence following antithrombotic therapy [9]. Cancer patients are also more likely to develop "unusual site" VTE, i.e., thrombosis that involves any venous segment outside the veins of the lower limbs and the pulmonary arteries, such as upper extremities, cerebral veins, caval vein, and splanchnic district (which encompasses the Budd–Chiari syndrome, portal vein thrombosis, mesenteric vein thrombosis, and splenic vein thrombosis) [10]. In patients with an active cancer, the risk of development of a DVT in the upper extremities is 18-fold higher compared to healthy subjects. In this unusual location, thrombosis occurs most often as a consequence of the placement of endovascular devices (i.e., central venous catheters) for administration of chemotherapy, antibiotics or nutrition [8]. Regarding splanchnic vein thrombosis, its association with neoplasms, especially hematological, is well recognized: myeloproliferative neoplasms are diagnosed in up to half of the patients with Budd–Chiari syndrome, and in one-third of those with extrahepatic portal vein obstruction [11].

Finally, in a significant proportion of patients with cancer, VTE is defined "incidental" or "unsuspected," because it is diagnosed as an incidental finding on computed tomography (CT) scans performed for other indications, typically staging or restaging of malignancy. The prevalence of incidental VTE is not rare: it has been estimated that the finding of an incidental PE in hospitalized cancer patients on routine radiographic studies of the chest is 4–9% [12]. In a study of pancreatic cancer patients, incidental VTE accounts for 33.3% of PEs, 21.4% of DVTs, and 100% of visceral VTEs [13]. It must be emphasized that the negative impact of incidental VTE on the prognosis of cancer patients does not differ from that of symptomatic VTE, with similar rates of recurrence, bleeding, and mortality [12].

Mechanisms

The association between thrombosis and cancer has been a subject of study for a longtime, starting from the pioneering researches of the French internist Armand Trousseau and the Viennese surgeon Theodor Billroth in the nineteenth century [14]. Cancer cells promote the activation of blood coagulation directly by generating thrombin, or indirectly by stimulating endothelial cells and circulating leukocytes and platelets to synthesize and express pro-coagulant factors [14]. On the other hand, proteins and cells involved in the hemostatic process may play a role in cancer progression [15]. As shown in Table 1, risk factors for cancer-associated thrombosis can be divided into three categories [16]. Regarding *patient-related factors*, in addition to demographic risk factors for VTE, such as age, gender, and race, cancer patients with a previous history of VTE, increased medical comorbidities, and those with specific issues such as infection, pulmonary disease, renal disease, and obesity have higher rates of VTE [16]. Among the *factors related to cancer itself*, the highest incidence of VTE is observed in patients with tumors originating in pancreas, stomach, brain, kidney, uterus, lung, and ovary as well as in patients with myeloma, lymphoma and leukemia, in particular in

Table 1 Clinical factors associated with increased risk of cancer-associated VTE (modified from Khorana et al. [16])

Cancer-related factors
Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma)
Histology (especially adenocarcinoma)
Advanced stage (metastatic)
Initial period after cancer diagnosis
Patient-related factors
Demographics: older age, female sex, African ethnicity
Comorbidities (infection, chronic kidney disease, pulmonary disease, atherothrombotic disease, obesity)
History of venous thromboembolism, inherited thrombophilia
Low performance status
Treatment-related factors
Major surgery
Hospitalization
Chemotherapy and anti-angiogenic agents
Hormonal therapy
Transfusion, central venous catheters

the first months after the diagnosis and in relation to the extension of the neoplasm and to the presence of metastasis [16]. Histological subtype also predicts the occurrence of cancer-associated VTE in some types of malignancy: for example, among patients with non-small-cell lung cancer, those with adenocarcinoma have a higher risk of developing VTE compared to subjects with squamous cell carcinoma [17]. Furthermore, *cancer therapies* themselves can increase the risk of VTE. Major surgery, immobilization associated with invasive procedures, placement of endovascular devices, such as central venous catheters, and, in general, hospitalization, are all factors related to an increased risk of VTE [7]. Regarding medical treatment of cancer, it has been estimated that the risk of VTE is 2–6 fold increase in patients undergoing systemic chemotherapy and that it is strictly related to the type of drug administered, being greater with anti-angiogenic agents, cisplatin, thalidomide and lenalidomide, in particular in combination with steroids or chemotherapeutic agents [12]. The mechanisms underlying the prothrombotic effects of cancer chemotherapy have only been partially elucidated and are likely to be multiple: anti-neoplastic drugs have been shown both to amplify the prothrombotic effect of cancer cells as well as causing a direct damage to vascular endothelium [14]. Moreover, supportive therapy, i.e., the use of the erythropoiesis-stimulating agents, as well as blood transfusions and steroids have also been associated with an increased risk of VTE [14, 15].

Strategies for prevention of VTE in patients with cancer

How can cancer patients be defined at high thromboembolic risk?

Although cancer patients are commonly considered at significant risk for VTE, this risk may be different in subgroups of this population, being the highest in: patients with metastatic disease, patients with pancreas, stomach, kidney, primary brain, uterus, lung, ovary cancer and patients with myeloma, lymphoma and leukemia, or during therapeutic interventions or surgery [4].

The recent guidelines for prevention and treatment of VTE in cancer patients released by the American Society of Clinical Oncology (ASCO) suggest that, to assess the level of risk and identify patients at "high risk" for thrombosis, "score systems" combining clinical and biological markers should be used [18]. The availability of predictive models facilitates the identification of patients at the highest risk, who have the greatest benefit/risk ratio from receiving antithrombotic pharmacological prophylaxis. The first "risk assessment model" (RAM) developed for cancer patients was the Khorana Score (Table 2), that is specific for patients undergoing chemotherapy [19]. This RAM is based on five predictive variables: cancer site, platelet count, hemoglobin level (or the use of erythropoiesis-stimulating agents), leukocyte count, and body mass index (BMI). This model, using a simple scoring system, has been shown to accurately predict the short-term risk of symptomatic VTE in patients undergoing chemotherapy, and has been validated in prospective and retrospective studies [3, 20–22]. The Vienna Cancer and Thrombosis Study (CATS) group expands the score by adding two thrombotic biomarkers (soluble P-selectin and D-dimer), showing that the risk prediction is considerably improved. Nevertheless, an important limitation of this score is the lack of simple availability of a serum P-selectin detection assay [21, 22].

Table 2 Khorana score

Patient characteristic	Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)	1
Platelet counts $\geq 350{,}000$ per mm^3	1
Leukocyte counts $> 11{,}000$ per mm^3	1
Haemoglobin < 10 g/dL or use of ESAs	1
BMI ≥ 35 kg/m^2	1

High risk: score ≥ 3

Intermediate risk: score 1 - 2

Low risk: score 0

BMI Body mass index, *ESAs* erythropoiesis-stimulating agents

More recently, a modified Khorana risk assessment score, the PROTECHT (Prophylaxis Thromboembolic Events Chemotherapy) score, was designed by adding platinum-(1 point) or gemcitabine-based (1 point) chemotherapy to the five original predictive variables for identifying high-risk patients in a post hoc analysis of the PROTECHT trial [23]. The clinical performance of this score is comparable to that of the original Khorana score [22]. Two new scores (ONCOTEV, COMPASS) have been proposed for ambulatory cancer patients undergoing chemotherapy, but they have not yet been validated [24, 25].

In the setting of multiple myeloma (MM), a RAM based on expert recommendation statements has been developed for the prevention of thalidomide and lenalidomide-associated thrombosis [26]. Finally, the Ottawa Score has been developed to identify, among cancer patients with thromboembolism, those at highest risk of recurrences, who may need prolonged anticoagulation [27]. The role of new thrombotic biomarkers (i.e., microparticle-associated tissue factor activity) to determine the individual risk of thromboembolism is under investigation [1, 2].

Prophylaxis of VTE in cancer patients hospitalized on internal medicine units for acute illnesses

There are no dedicated randomized clinical trials on antithrombotic prophylaxis in hospitalized cancer patients. The available trials in this setting enroll hospitalized medically ill patients of whom a variable proportion are patients with a history of cancer [28–31].

However, the current guidelines, influenced by trials on prophylaxis in medically ill patients [29–31], and based on the fact that active cancer is a strong risk factor for VTE, clearly recommend pharmacological prophylaxis throughout hospitalization in high-risk cancer patients with acute medical illnesses, in the absence of bleeding or other contraindications [18, 32–34]. Multiple scoring systems to predict in-patient VTE currently exist; in particular, the Padua Prediction Score (PPS) is widely recommended [35] in the setting of hospitalized cancer patients [18]. Unfortunately although PPS and other tools include an active diagnosis of cancer as a variable, these scores have been derived from populations of medically ill hospitalized patients, and they have not been validated specifically for hospitalized cancer patients. Moreover, the standard pharmacological prophylaxis, evaluated in trials on prophylaxis in medically ill in-patients (enoxaparin 40 mg, dalteparin 5000 IU, fondaparinux 2.5 mg), does not reduce the overall rate of VTE compared with placebo in a review on 307 cancer patients, and the recommended doses may be suboptimal for this high-risk population [36, 37]. Recently Patell et al., in a retrospective study, also validate the Khorana score as a tool to predict VTE in hospitalized cancer patients [38]. The authors find that this score is significantly associated with the risk of in-patient VTE [38]. Further studies to compare the performance of Khorana score with other risk assessment tools in hospitalized cancer patients and to incorporate thrombotic biomarkers to improve risk assessment are needed. Dedicated studies are also needed to re-evaluate the benefit of prolonging pharmacological prophylaxis after hospital discharge, considering that cancer patients may remain at high risk of VTE after hospitalization. The pharmacological prophylaxis extended to another 28 days, after the standard 10 days, significantly increases the bleeding risk in the EXCLAIM study, with a non-statistically significant reduction of rate of VTE in the subgroups of cancer patients [39]. Finally, further evidence should be obtained with the DOACs that are not licensed for prophylaxis in medical in-patients with cancer [40, 41].

The role of non-pharmacological primary VTE prophylaxis in high bleeding risk neoplasms, and in case of thrombocytopenia

Bleeding risk Cancer patients are exposed to a high bleeding risk because of possible thrombocytopenia (resulting from chemotherapy) or other cancer-related characteristics, such as the site of the disease (i.e., primary brain tumors). In cases of active bleeding or of a high risk of bleeding, most guidelines do not recommend anticoagulation and suggest the use of mechanical prophylaxis, in the form of pneumatic compression devices or graduated compression stockings (GCS) [18, 34]. However, there are no studies including only patients with cancer for mechanical prophylaxis. Mechanical prophylaxis seems to be effective in reducing post-operative VTE, but evidence in the medical setting is controversial [36]. However, based on extrapolation of data from these populations, mechanical prophylaxis should be considered in hospitalized patients with active cancer and concomitant active bleeding or high risk of bleeding until the bleeding risk decreases.

Thrombocytopenia Pharmacological primary prophylaxis should be continued in case of mild thrombocytopenia, when the platelet count is $\geq 50{,}000/mm^3$. If the platelet count is between $25{,}000/mm^3$ and $50{,}000/mm^3$, pharmacological prophylaxis should be decided on an individualized basis. According to guidance from the SSC of the International Society of Haemostasis and Thrombosis (ISTH), and in the absence of clear evidence on platelet cutoffs, pharmacological primary prophylaxis should be avoided and mechanical prophylaxis utilized, in patients with a platelet count of $< 25{,}000/mmc$ [36].

Primary VTE prophylaxis in surgery for cancer

All patients with malignancy undergoing major surgical interventions should be considered for pharmacological prophylaxis because, compared with non-cancer patients, those with malignancy have a 2–3-fold higher risk for VTE during the peri-operative period [3]. However, activation of the coagulation system is known to persist in the post-operative period, beyond the first 7–10 days following surgery. Multiple studies and meta-analyses [42–45] have compared the safety and efficacy of extended-duration VTE prophylaxis, i.e., for 3–4 weeks after surgery, with in-hospital prophylaxis in major abdominal or pelvic oncologic surgery. The results favor extended duration prophylaxis in terms of reducing the incidence of thromboembolic events with no significant differences in outcomes such as major bleeding and death. Based on the available data, current ASCO and National Comprehensive Cancer Network (NCCN) guidelines recommend that anticoagulants should be continued for 7–10 days in all patients, with the exception of patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors, in whom VTE prophylaxis should be continued for up to 4 weeks. On the other hand, the European Society of Medical Oncology (ESMO) guidelines recommend a prolonged prophylaxis for all cancer patients undergoing major abdominal

or pelvic surgery. Finally, the American College of Chest Physicians (ACCP) guidelines recommend that ''high-risk VTE patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk of major bleeding complications'' should receive pharmacologic prophylaxis with LMWH for 4 weeks postoperatively, but recommend assessment of both VTE and bleeding risk before starting therapy [18, 32, 33, 46]. Unfortunately, there are no validated scores to assess thrombotic or hemorrhagic risk in this specific surgical setting, and an individual evaluation of the patient remains of primary importance.

Primary VTE prophylaxis in cancer outpatients

Several studies have focused on prophylaxis in the ambulatory cancer population. The PROTECHT (Prophylaxis Thromboembolic Events Chemotherapy) trial randomly assigned patients with metastatic or locally advanced lung, breast, gastrointestinal, ovarian, or head and neck cancer to receive daily subcutaneous (SC) nadroparin (3800 IU) or placebo. Rates of VTE in high-risk patients were 11.1% with placebo and 4.5% with nadroparin (NNT 15 vs. 77 in low- and intermediate risk patients) [23]. Similarly, the SAVE-ONCO trial randomly assigned patients with metastatic or locally advanced solid tumors during chemotherapy to receive semuloparin or placebo. This study demonstrates a significant reduction in the incidence of VTE in patients receiving semuloparin (1.2%), with no apparent increase in the incidence of major bleeding [47]. A subgroup analysis of the SAVE-ONCO study shows an NNT of 25 for high-risk patients and of 333 for low-risk patients, with no significant difference in the rates of bleeding between the two groups, suggesting the need to stratify the thromboembolic risk before initiating prophylaxis in ambulatory cancer patients to obtain the greatest benefit/risk ratio. Similarly, studies addressing specific high-risk tumors have demonstrated a profound benefit of anticoagulation in high-risk populations. The FRAGEM study (A Phase II Randomized Study of Chemo-Anticoagulation [Gemcitabine–Dalteparin] Versus Chemotherapy Alone [Gemcitabine] for Locally Advanced and Metastatic Pancreatic Adenocarcinoma) focused on patients with pancreatic cancer, and demonstrates a reduction in the rate of VTE from 23% in the placebo arm to 3.4% in the prophylaxis arm (NNT 6) [48]. The PROSPECT-CONKO 004 trial also addressed patients with pancreatic cancer finding a reduction in the rate of VTE from 9.87 to 1.25% at 3 months and from 15.13 to 5% at 12 months [49]. In patients with MM treated with lenalidomide, aspirin and low-molecular-weight heparin (LMWH) demonstrate a similar benefit in reducing the incidence of VTE [2, 3].

Based on the results of available trials, the current guidelines [18, 32–34] do not recommend routine pharmacological prophylaxis in cancer outpatients who have no additional risk factors for VTE. Clinicians should consider anticoagulant prophylaxis in selected patients at high VTE risk receiving chemotherapy, based on the thrombotic risk assessment [18].

Ongoing trials are assessing the safety and efficacy of DOACs in ambulatory patients with cancer [50, 51]. The CASSINI trial will compare rivaroxaban 10 mg versus placebo for up to 6 months in adult ambulatory cancer patients (NCT02555878) [50]. The AVERT trial (NCT02048865) will evaluate low dose apixaban (2.5 mg BID) versus placebo [51].

Key points

- Patients with cancer are at increased risk of VTE, in the presence of multiple predisposing factors (patient-related risk factors and factors related to cancer itself). The risk of VTE may be different in subgroups of this population. To assess the level of risk and identify patients at "high risk" for thrombosis, the use of "score systems" combining clinical and laboratory markers is recommended.
- In the absence of bleeding or other contraindications, cancer patients hospitalized for acute medical illness should receive pharmacological prophylaxis.
- Mechanical prophylaxis should be considered in hospitalized patients with active cancer and concomitant active bleeding or at high risk of bleeding, until the bleeding risk decreases, and in patients with a platelet count of $< 25{,}000$/mmc.
- Anticoagulant prophylaxis is recommended for all patients undergoing major surgery for cancer, with extended prophylaxis (for up to 4 weeks) in major abdominal or pelvic surgery in patients who are not otherwise at high risk of major bleeding complications.
- Clinicians should consider primary anticoagulant prophylaxis in selected ambulatory patients at high VTE risk receiving chemotherapy, based on the thrombotic risk assessment.

Treatment of VTE in patients with cancer

What is the optimal treatment of acute VTE in cancer patients?

Except for selected patients requiring aggressive treatments, the large majority of cancer patients should be treated with therapeutic doses of LMWH, unfractionated heparin (UFH) or fondaparinux. A recent Cochrane meta-analysis of 15 studies, where participants with cancer represented subgroups were studied, shows that in the initial treatment of VTE, LMWHs and UFH might have a different comparative efficacy in people with cancer than in people without

cancer [52]. Among 13 studies comparing LMWH to UFH, LMWH likely decreases mortality at 3 months compared to UFH (RR 0.66, 95% CI 0.40–1.10), but does not rule out a clinically significant increase or decrease in VTE recurrence. A study comparing fondaparinux with heparin (UFH or LMWH) [53] cannot exclude a beneficial or detrimental effect of fondaparinux on mortality at 3 months (RR 1.25, 95% CI 0.86–1.81). A study comparing dalteparin with tinzaparin [54] cannot exclude a beneficial or detrimental effect of dalteparin on mortality (RR 0.86, 95% CI 0.43–1.73), VTE recurrence, major or minor bleeding. Thus, LMWH is possibly superior to UFH in reducing mortality in the initial treatment of VTE in people with cancer. The confidence in this effect is reduced by both the risk of bias in included studies, and the likelihood of publication bias. However, there are additional advantages of LMWH related to SC administration in outpatient management [55]. The 2016 International Initiative on Thrombosis and Cancer (ITAC-CME) clinical practice guidelines state that LMWH is recommended for the initial treatment of VTE in patients with cancer (Grade 1B), but fondaparinux and UFH can also be used [2]. The ASCO guidelines [18] suggest dosing regimens for the initial treatment of VTE in patients with malignancy: UFH 80 U/kg intravenous (IV) bolus, then 18 U/kg per hour IV, with dose adjustment based on aPTT, dalteparin 100 U/kg every 12 h or 200 U/kg once daily, enoxaparin 1 mg/kg every 12 h or 1.5 mg/kg once daily, tinzaparin 175 U/kg once daily, fondaparinux 5, 7.5 or 10 mg once daily according to body weight (< 50 kg, 50–100 kg, > 100 kg).

What is the role of LMWH and vitamin K antagonists (VKA) after the acute phase?

LMWHs have been the standard treatment in the long-term management of cancer-associated thrombosis over the last 15 years. In a landmark study (CLOT trial), 672 patients with cancer and acute symptomatic VTE were randomly assigned to receive dalteparin at a dose of 200 IU/kg SC once daily for 5–7 days and a coumarin derivative for 6 months or dalteparin alone for 6 months (200 IU/kg once daily for 1 month, followed by a daily dose of 150 IU/kg for 5 months) [56]. During the 6-month study period, 8.0% of patients in the dalteparin group have recurrent VTE compared to 15.8% of patients in the coumarin group [hazard ratio (HR) 0.48; 95% confidence interval (CI) 0.30–0.77, $p = 0.002$]. No significant difference is observed between the two groups in the rates of major bleeding or any bleeding [56]. These results are not confirmed by other smaller size studies on LMWH versus warfarin, such as the CANTHANOX [57] and the CATCH studies, which fail to demonstrate the superiority of LMWHs in preventing VTE recurrence [58]. Currently, LMWHs are recommended as first-line therapy for the short- and long-term management of cancer-associated VTE by different international guidelines, including those of ESMO [33], ACCP [59], ASCO [18] and NCCN [60]. However, the requirement of daily SC injections makes LWMH inconvenient to use, and compliance is an issue in some patients. Moreover, aside from their problematic use in renal insufficiency due to the reduced renal clearance, cost is an obstacle that limits their use in many countries. Although heparin-induced thrombocytopenia (HIT) occurs at a lower rate with LMWHs when compared to UFH, it constitutes a high risk in terms of morbidity and mortality. On the other hand, VKA, although not recommended as the preferred treatment in cancer VTE patients, are still widely used, given the oral route of administration and the relatively low cost: many clinicians are still prescribing warfarin or are using DOACs off-label in cancer-associated VTE patients. In a retrospective analysis of a large administrative database including over 100,000 patients with cancer-associated VTE, oral agents, with particular reference to warfarin, are the most commonly prescribed anticoagulants, with DOACs prescribed in 10% of patients and LMWH in approximately 40% [61].

What is the role of DOACs after the acute phase?

Over the past few years, DOACs were thoroughly investigated in the acute treatment of both DVT and PE. Evidence on the use of DOACs in cancer patients until recently has been limited, because mainly extrapolated from subgroup analyses of patients with cancer [62] (Table 3). Meta-analyses of these studies report no significant differences between DOACs and warfarin in terms of recurrent VTE and major bleeding [63–66], but these are based on indirect comparisons. Actually, no randomized trials with DOACs in this specific population were available. The Hokusai VTE Cancer trial, an open-label, non-inferiority study, is the first randomized trial that has compared a DOAC (edoxaban) to an LMWH (dalteparin) in patients with cancer-associated VTE [67]. The trial enrolled 1050 patients, predominantly affected by advanced cancer, with acute symptomatic or incidental DVT or PE. Patients were randomized to edoxaban 60 mg daily (dose adjusted according to renal function and body weight), preceded by LMWH (physician choice) initially for at least 5 days, or to dalteparin 200 IU/kg SC once daily for 30 days with a maximum daily dose of 18,000 IU. Then, dalteparin was given at a dose of 150 IU/kg once daily. The randomized treatment was given for at least 6 months, and the minimum duration of follow-up was 9 months. The primary endpoint, the composite of the first recurrent VTE or major bleeding within 12 months, occurs in 12.8% of patients in the edoxaban arm compared to 13.5% in the dalteparin arm (HR with edoxaban 0.97, $p = 0.006$ for non-inferiority). Major bleeding occurs in 6.9% of patients

Table 3 Subgroup analysis of patients with cancer in the large trials on DOACs for the treatment of VTE (modified from Imberti et al. [62])

Trial, year of publication	Comparator	Study drug	VTE	(%) (*N*)	Major bleeding	% (N)
			Comparator	Study drug	Comparator	Study drug
EINSTEIN (PE + DVT), 2014	LMWH + Warfarin	Rivaroxaban	4.0 (8/198)	2.6 (6/232)	4.1 (8/196)	2.6 (6/232)
AMPLIFY, 2015	LMWH + Warfarin	Apixaban	6.4 (5/78)	3.7 (3/81)	5 (4/80)	2.3 (2/87)
RECOVER (I, II), 2015	LMWH + Warfarin	Dabigatran	7.4 (12/162)	5.6 (10/173)	4.6 (7/152)	3.8 (6/159)
Hokusai-VTE, 2016	LMWH + Warfarin	Edoxaban	7.1 (7/99)	3.7 (4/109)	3.0 (3/99)	4.6 (5/109)

in the edoxaban arm as compared to 4.0% in the dalteparin arm (HR 1.77, $p = 0.04$), with gastrointestinal cancer being more likely associated with major bleeding with edoxaban compared to dalteparin (13.2% vs 2.4%, respectively, $p = 0.0169$) [67].

Another similar study has been recently published, the Select-D pilot trial [68]. This is a multicenter, randomized, open-label, trial, performed in the United Kingdom, that evaluated patients with active cancer and symptomatic/incidental PE or lower-extremity proximal DVT, treated with dalteparin (200 IU/kg daily during month 1, then 150 IU/kg daily for months 2–6) (203 patients) or rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months) (203 patients). The primary outcome is VTE recurrence over 6 months. Safety was assessed by major bleeding and clinically relevant nonmajor bleeding (CRNMB). The 6-month cumulative VTE recurrence rate is 11% with dalteparin and 4% with rivaroxaban (HR 0.43; 95% CI 0.19–0.99). The 6-month cumulative rate of major bleeding is 4% for dalteparin and 6% for rivaroxaban (HR, 1.83; 95% CI 0.68–4.96). Rates of CRNMB are 4% and 13%, respectively (HR, 3.76; 95% CI 1.63–8.69) [68]. A meta-analysis of these two trials reveals that DOACs have a lower 6-month recurrent VTE (42/725) when compared to LMWH (64/727) [RR: 0.65 (0.42–1.01)] [69]. However, DOACs have a higher incidence of major bleeding (40/725) when compared to LMWH (23/727) [RR 1.74 (1.05–2.88)]. Similarly, the risk of CRNMB is higher [RR 2.31 (0.85–6.28)] for patients receiving DOACs. The most major bleeding events are gastrointestinal, and there are no central nervous system bleedings. Patients with esophageal or gastroesophageal cancer tend to experience more major bleedings with DOACs than with dalteparin. There is no difference in mortality [RR 1.03 (0.85–1.26)] [69]. While the cumulative data from trials evaluating the safety and efficacy of DOACs suggest a role for their use in cancer-associated VTE, it remains to be seen whether the favorable outcomes of edoxaban and rivaroxaban use in cancer patients with VTE represent a class effect for all DOACs.

Despite these favorable results, there are no data on the differential activity of DOACs in specific subtypes of cancers and treatments. DOACs might have significant interactions with many of the chemotherapeutic agents or other supplementary drugs used in cancer patients, namely the antifungal azole agents. Several ongoing clinical trials are testing the efficacy and safety of DOACs specifically in cancer patients [62] (Table 4).

The 2016 update of the ITAC-CME 2013 guidelines states that DOACs can be considered for early maintenance (10 days–3 months) and long-term therapy (> 3 months) in patients with VTE and stable cancer not receiving anti-cancer therapy [2]. The 2016 update of the 9th edition ACCP Guidelines on Antithrombotic Therapy for VTE Disease [59, 70] suggests LMWH over DOACs with a low rating of the quality of evidence (Grade 2C) for long-term (first 3 months) anticoagulant therapy in patients with cancer-associated VTE. A recent update of the NCCN guidelines gives a level 1 of evidence to edoxaban [60]. An individualized treatment is recommended in a recently published guidance from the SSC of the ISTH [71] that suggests the use of specific DOACs in cancer patients with acute VTE and low risk of bleeding, after shared decision making with patients. Further guidelines incorporating the latest clinical studies are anticipated in the next future.

Despite scarce evidence in the specific setting until recently, the use of DOACs in patients with cancer-associated VTE has been rapidly increasing in clinical practice, especially in those with non-gastrointestinal and non-lung cancer, and in those not receiving chemotherapy, given the additional uncertainty related to drug interaction.

While waiting for novel guidelines incorporating current and future evidence on DOACs, clinicians should choose the most suitable drug for the individual patient, taking into account patients' preferences and their compliance, which may be the most powerful determinant of clinical benefit.

What is the appropriate dose and duration of anticoagulation for the long-term treatment and secondary prevention?

After discontinuation of antithrombotic treatment, cancer-associated VTE has a risk for recurrences that is almost twice as high as that observed in patients free from malignancies [72]. In the absence of well-designed studies evaluating the efficacy, safety and cost-effectiveness of continuing anticoagulant therapy beyond the acute treatment period of

Table 4 Current ongoing studies with DOACs in cancer patients with VTE (modified from Imberti et al. [62])

Title, trial number	Study design	PHASE	Condition	Study drug	Comparator
CONKO_011/AIO-SUP 0115/ Ass.: Rivaroxaban in the treatment of venous thromboembolism (VTE) in cancer patients—a randomized phase III study (NCT02583191)	RCT	III	VTE	Rivaroxaban	LMWH
Non-interventional study on Xarelto for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in patients with active cancer (COSIMO) (NCT027426239)	Prospective cohort	III	DVT and PE	Rivaroxaban	
Apixaban for the treatment of venous thromboembolism in patients with cancer (CARAVAGGIO) NCT03045406	RCT	III	VTE	Apixaban	LMWH
Rivaroxaban utilization for treatment and prevention of thromboembolism in cancer patients: experience at a comprehensive cancer center (NCT02502396)	Retrospective Cohort	Not applicable	DVT of the lower and upper extremities PE NVAF	Rivaroxaban	
Cancer-associated thrombosis, a pilot treatment study using rivaroxaban (CASTA-DIVA) (NCT02746185)	RCT	III	VTE	Rivaroxaban	LMWH
DOACs vs LMWH +/_warfarin for VTE in cancer: a randomized effectiveness trial (CANVAS TriaL (NCT02744092)	RCT	Not applicable	Cumulative VTE recurrence	Apixaban Dabigatran Edoxaban Rivaroxaban	LMWH alone or with warfarin
Study of dabigatran etexilate as primary treatment of malignancy-associated venous thromboembolism (NCT03240120)	RCT	III	VTE	Dabigatran etexilate	Tinzaparin
Randomized phase II study to compare the safety and efficacy of dalteparin vs. rivaroxaban for cancer-associated venous thromboembolism (PRIORITY) NCT03139487	RCT	II	VTE	Rivaroxaban	Dalteparin
Apixaban as treatment of venous thrombosis in patients with cancer: the CAP study (CAP) (NCT02581176)	Single group assignment	IV	VTE	Apixaban	

3–6 months, evidence-based recommendations about the optimal duration of anticoagulation in this setting are lacking. Consensus guidelines generally suggest continuing anticoagulation in patients with active cancer or receiving cancer treatment, with periodic reassessment of the risks and benefits [72]. Several factors need to be individually evaluated. The choice of duration should take into account the risk of VTE recurrence, the risk of bleeding, and patients' preferences and values. Anticoagulants may increase the severity of any bleeding by interfering with hemostasis, translating to a higher risk of bleeding in this setting, related to the risk for malignant vascular or mucosal invasion and cancer- or chemotherapy-induced thrombocytopenia. From randomized controlled trials performed exclusively in cancer patients, the incidence of major bleeding ranges from 4.6 to 11.6% during the first 3–6 months of anticoagulation [62], with even higher bleeding rates in the real-world setting [72, 73]. Overall, the risk of clinically important bleeding with

anticoagulation is highest during the first month of therapy, but is lower thereafter at approximately 0.5% per month while on anticoagulation [72, 73]. The risk appears to be independent of the type of anticoagulant and the intensity of anticoagulation, but varies with patient- and cancer-specific comorbidities.

Cancer patients have a three to fourfold higher risk of recurrent VTE during anticoagulant therapy than cancer-free patients. In the CLOT and CATCH trials, the 6-month incidence of symptomatic, recurrent VTE in the LMWH groups is 6% and 7.2%, respectively [56, 58]. The risk is highest in the first month at 5.7%, dropping down to 3.4% during months 2–6 and 4.1% during months 7–12. A number of clinical features have been identified to correlate with a higher risk of recurrent cancer-associated VTE, including extensive and metastatic cancer, and lung cancer [74]. Overall, in the Rochester Epidemiology project database, the adjusted cumulative risks of recurrence vs major bleeding are 16.6% vs 2.0% at 6 months and 19.6% vs 4.0% at 1 year [75]. Thus, the case fatality of bleeding must be at least 5- to 8-fold higher than that of recurrent VTE in order to justify stopping anticoagulation.

The DALTECAN [76] and TiCAT [77] studies, single-arm cohort studies treating cancer VTE patients with dalteparin (DALTECAN) or tinzaparin (TiCAT) for more than 6 months (12 months), show that the risk of recurrent thrombosis or major bleeding is higher during the first 3–6 months of treatment, with an ongoing risk of VTE recurrences beyond 6 months, supporting the use of parenteral anticoagulation beyond 6 months in cancer patients. On the other hand, whatever the drug chosen, treatment for cancer-associated VTE is also burdensome for patients. In general, prolongation of anticoagulation beyond 3–6 months should be considered for as long as the malignant disorder is active, if not contraindicated. This often translates into life-long anticoagulation [78]. Metastatic disease or progressive cancer, ongoing chemotherapy or a thrombogenic regimen (e.g., immunomodulatory drugs, dexamethasone, tamoxifen), pancreatic, upper gastrointestinal (e.g., esophageal, stomach, cholangiocarcinoma), lung or ovarian cancer, glioblastoma, myeloproliferative neoplasm, or a previous history of VTE shift the balance versus prolongation. Before switching to an oral agent, drug interactions, liver and renal dysfunction, and diet or gastrointestinal concerns should be addressed. The decision should be periodically reassessed. Patients with bleeding or thrombocytopenia should receive LMWH dose adjustment [78, 79]. For extended anticoagulation, the 2016 ACCP guidelines suggest using LMWH over oral agents in patients with cancer, with no preference for VKA or DOAC, or any one DOAC over another DOAC [59]. These recommendations may change based on the new evidence from Hokusai cancer trial and Select-D [67–69], showing that, after the initial 3-month treatment period and until 12 months, the risks of recurrent VTE and major bleeding are similar for LMWH and DOAC, whereas previous studies have reported that they are higher for VKAs. Thus, while the efficacy and safety of LMWH in this specific setting are restricted to the first 6 months of treatment, the benefits of DOACs have been verified over a longer time period.

What is the appropriate treatment strategy for recurrent VTE in cancer patients during anticoagulation?

Recurrent VTE despite appropriate anticoagulation is common among cancer patients [80]. Reasons for recurrent VTE may include lack of compliance, temporary cessation of therapy due to bleeding or procedures, inadequate dosing, cancer progression, and the occurrence of HIT [81]. Unfortunately, there are no randomized trials to provide an evidence-based approach. A paper and an ISTH guidance statement have described empirical approaches to this clinical problem [79, 80]. In general, LMWH monotherapy is considered the preferred approach. If patients are already on LMWH, dose escalation should be considered [81]. The guidance statement suggests that cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with an agent other than LMWH be transitioned to therapeutic LMWH, assuming no contraindications to LMWH [79]. The ACCP guidelines suggest switching to treatment with LMWH, at least temporarily, in patients with recurrent VTE on VKA (in therapeutic range) or on DOACs (and who are believed to be compliant and assume the therapeutic recommended doses) [59]. Cancer patients with symptomatic recurrent VTE despite optimal anticoagulation with LMWH continue with LMWH at a higher dose, starting with an increase of 25% of the current dose or resuming the therapeutic weight-adjusted dose if the patient has been receiving a non-therapeutic dose at the time of recurrence. In case of symptomatic improvement, the same dose of LMWH should be continued and usual follow-up should be resumed. In patients without symptomatic improvement, further escalation may be undertaken, based on the peak anti-Xa level [79].

Use of vena caval filters should be discouraged except in the presence of absolute contraindications to anticoagulation (e.g., active bleeding). If necessary, retrievable filters should be used, and a plan created to retrieve the filter when appropriate [4].

When to treat incidental VTE?

Incidental VTE, defined as VTE discovered on scans ordered for reasons other than suspected VTE (typically cancer staging or restaging), is an emerging major contributor to the burden of cancer-associated VTE. The majority of incidental

VTE in malignancy involves visceral veins [13]. Visceral vein thrombi include portal, mesenteric, splenic, renal and gonadal vein thrombi. In a cohort study of gastrointestinal cancer patients, 100% of visceral vein thrombi are incidentally discovered compared to 35% of PE [82]. Although management of these events remains controversial, retrospective studies and registries have found similar risks of mortality and recurrent VTE between patients with symptomatic and incidental PE [11, 13, 83–85]. Accordingly, international guidelines recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic PE [59]. However, there is some evidence that patients with isolated, incidental subsegmental PE may not need anticoagulant treatment [86]. According to most of the currently available guidelines, including those of ASCO [18], treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.

Key points

- For the treatment of acute VTE in cancer patients, LMWH is indicated for 5–10 days, but fondaparinux and UFH can also be used.
- LMWHs are also recommended as first-line therapy for the long-term management of cancer-associated VTE. However, the available data from trials evaluating the safety and efficacy of edoxaban and rivaroxaban suggest their use in cancer-associated VTE at low bleeding risk. While waiting for novel guidelines incorporating current and future evidence on DOACs, clinicians should choose the most suitable drug for the individual patient, taking into account patients' preferences and compliance.
- Anticoagulation should be extended beyond 6 months in patients with active cancer or receiving cancer treatments, with periodic reassessment of the risks and benefits.
- Cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with an agent other than LMWH should be transitioned to therapeutic LMWH. Patients with symptomatic recurrent VTE despite optimal anticoagulation with LMWH should continue with LMWH at a higher dose, starting with an increase of 25% of the current dose or resuming the therapeutic weight-adjusted dose if the patient is receiving a non-therapeutic dose at the time of recurrence. In case of symptomatic improvement, the same dose of LMWH should be continued and usual follow-up should be resumed. In patients without symptomatic improvement, further escalation may be undertaken, based on the peak anti-Xa level.
- Incidental VTE in cancer patients should be treated with therapeutic anticoagulation, with the exception of isolated subsegmental PE. Treatment of incidental splanchnic vein thrombosis should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.

Management of anticoagulant drugs in patients with cancer

How anticoagulation should be managed in cancer patients with kidney disease or advanced liver disease?

LMWH is cleared by the kidneys and has a significant accumulative effect in patients with impaired renal function [creatinine clearance (CrCl) < 30 mL/min]. Indeed, patients with CrCl < 30 mL/min who are treated with standard therapeutic doses of enoxaparin have elevated levels of anti-Xa activity and an increased risk of major bleeding. In patients with severe renal failure (CrCl < 30 mL/min), IV UFH (or SC UFH as an alternative option) or LMWH with anti-Xa activity monitoring are recommended [33, 59]. On the contrary, LMWH, due to its kidney clearance, is quite safe in case of liver diseases. As far as DOACs are concerned, the anti-Xa edoxaban is the only one that has been studied in the setting of cancer VTE treatment at a reduced dose of 30 mg for patients with impaired renal function in the Hokusai VTE Cancer study [87]; hence, it could be reasonable to use a reduced dose of edoxaban in patients with CrCl in the range 30–50 mL/min. In the case of liver disease, it is possible to use DOACs that were studied in the setting of cancer such as edoxaban [67] and rivaroxaban [68]. In particular, in patients with a Child–Pugh class A, edoxaban and rivaroxaban are an acceptable option, whereas in case of Child–Pugh class B and C, DOACs are not proven to be safe [88]. Noteworthy, for patients with mild liver disease, the use of DOACs is acceptable as it is not associated with an increased risk of bleeding [89].

How relevant are pharmacokinetic and pharmacodynamic interactions in cancer patients with VTE?

Polypharmacy is a well-established risk factor for adverse events resulting from drug interactions, and this issue is particularly relevant in the setting of cancer. Thus, chemotherapy consists of a large scenario of different drugs with several interactions with liver metabolism. Whereas LMWHs have few drug–drug interactions, DOACs interact with several drugs [90, 91]. In particular, all the drugs that use as a substrate P-glycoprotein (P-gp) and CYP3A4 are known to interfere with DOACs. The recent update of the European Heart Rhythm Association (EHRA) practical guidelines provides a simple and detailed guide to deal

with important drug interactions [91], and a complete list of interfering drugs was reported by Short NJ et al. [90]. In summary, among the antimitotic agents, Vinblastine, among the Anthracyclines, Doxorubicin, among the tyrosine kinase inhibitors, Vandetanib and Sunitinib, and, among the immune-modulators, dexamethasone significantly reduce DOACs plasma concentrations. On the contrary, plasma DOACs concentrations are increased by the hormonal agents Abiraterone and Enzalumide, and by the Tyrosin Kinase inhibitors Imatinib and Crizotinib [90, 91]. The list of drug interactions is expected to be significantly enriched over the next years.

How thrombocytopenia may change the approach to cancer patients with acute VTE?

The optimal management of hematologic malignancy-associated VTE in patients with moderate-to-severe thrombocytopenia is unclear. A full-dose anticoagulation is safe when platelet count is above 50×10^9/L [92]. On the contrary, the management of patients who requires anticoagulation during periods of severe thrombocytopenia (platelets $<50\times10^9$/L), especially for those requiring a therapy for more than a few days, is uncertain. According to the recent recommendations from the SSC of the ISTH [93], two management strategies can be proposed.

1. Full-dose anticoagulation with transfusion support.
2. Dose-modified anticoagulation while platelets are $<50\times10^9$/L [94].

Studies assessing the use of full-dose anticoagulation in combination with transfusion support usually use a platelet transfusion threshold of $40–50\times10^9$/L, but this cutoff is supported only by a consensus and scientific prospective data on this issue are still lacking [95]. The dose modification strategy derived from expert consensus employs different approaches, including empirical reductions in dosing to prophylactic or half-therapeutic doses. A recent systematic review on this issue fails to identify any evidence for superiority of one approach over another [93]. The most recent evidence supports the following suggestions for the acute phase:

- For patients with acute cancer-associated VTE in the presence of symptomatic segmental or more proximal PE, proximal DVT, or a history of recurrent/progressive thrombosis, therapeutic doses of anticoagulation with platelet transfusion support to maintain platelet counts above $40–50\times10^9$/L may be considered.
- For patients with lower risk events (e.g., distal DVT, incidental sub segmental PE and catheter-related), a dose modification strategy using 50% of therapeutic, or the prophylactic LMWH dose, for platelets $25–50\times10^9$/L may be considered.
- Anticoagulation should be discontinued for platelet counts 25×10^9/L although prophylactic doses might be reasonable in patients with acute VTE and a platelet count $>10\times10^9$/L.

The most recent evidence supports the following suggestions for the Chronic phase.

- The risk of recurrence decreases after the initial 30-day period. Hence, in this subacute or chronic period, a lower dose of anticoagulants should be given in order to lower the risk of bleeding. In particular, decreased dosing (50% or prophylactic doses of LMWH) for platelet counts between $25–50\times10^9$/L and temporary discontinuation for platelets $<25\times10^9$/L should be considered. LMWH is still to be the preferred as anticoagulant among patients with cancer-associated VTE and thrombocytopenia, as data on the use of DOACs in cancer patients with severe thrombocytopenia ($<50\times10^9$/L) are lacking.

How to ensure adherence to anticoagulant drugs in cancer patients?

Treatment with LMWH is associated with a high rate of discontinuation. This issue was recently investigated by Van der Wall et al. [96] who find a discontinuation rate of 51% (21% due to side effects) at 6 months analyzing a population of 372 patients with active cancer and VTE. Female gender is the only factor found to be associated with premature discontinuation. Hence, it is difficult to imagine a score able to predict the discontinuation rate in this setting. For DOACs, we have no data concerning compliance in the setting of cancer patients. It is arguable that the rules applicable to the general population in order to ensure compliance with therapy are also valid for cancer patients [96]. Patient education on the need for anticoagulant therapy and the relevance of strict compliance are important. Several simultaneous approaches can be employed to support patients' compliance. In particular, leaflets and instructions at initiation of therapy, a patient anticoagulation card, group sessions, and re-education at every prescription renewal might improve the compliance [91, 97].

Key points

- In patients with severe renal failure (CrCl < 30 mL/min), IV UFH (or SC UFH as an alternative option) or LMWH with anti-Xa activity monitoring is recommended. It might be reasonable to use a reduced dose of edoxaban in patients with CrCl in the range 30–50 mL/min.

- LMWH, due to its kidney clearance, is quite safe in case of liver diseases. In patients with a Child–Pugh class A, edoxaban and rivaroxaban are acceptable options whereas in case of Child–Pugh class B and C, DOACs are not proven to be safe.
- In cancer patients with thrombocytopenia and acute VTE, or a history of recurrent/progressive thrombosis, therapeutic doses of anticoagulation with platelet transfusion support to maintain platelet counts above $40–50 \times 10^9$/L may be considered. For patients with lower risk events (e.g., distal DVT, incidental sub segmental PE and catheter-related), a dose modification strategy using 50% of therapeutic, or the prophylactic LMWH dose, for platelets $25–50 \times 10^9$/L may be considered. Anticoagulation should be discontinued for platelet counts $< 25 \times 10^9$/L although prophylactic doses might be reasonable in patients with acute VTE and a platelet count $> 10 \times 10^9$/L. For subacute or chronic VTE, the LMWH dose should be reduced in patients with platelet count $< 50 \times 10^9$/L, and stopped if the platelet count is $< 25 \times 10^9$/L. Data on the use of DOACs in cancer patients with platelet counts $< 50 \times 10^9$/L are lacking.

Management of bleeding complications in cancer patients with VTE

When approaching a cancer patient who bleeds while taking an anticoagulant drug, a precise clinical history (focused on medical history, any comedication, type, dose, and time to last taken dose of the anticoagulant drug), and an accurate physical examination (including the evaluation of hemodynamic and neurologic state) are mandatory. Then, biochemical and, if indicated, imaging studies might help physicians to classify the type of bleeding. In fact, minor bleeding, such as mild nose and gum bleeds, menorrhagia, ecchymosis or minor wound, can be managed without interruption or with minimal variation of the anticoagulant treatment (i.e., reducing, delaying or skipping one dose of the drug); on the other hand, in all cases of major bleeding and in almost all cases of CRNMB, the discontinuation of anticoagulant therapy is needed [98]. Regardless of the anticoagulant drug used, general supportive measures for the treatment of bleeding include, first of all, local hemostasis and mechanical compression of the source of bleeding, administration of antifibrinolytic agents, and, if indicated, hemodynamic support with intravenous fluids, and transfusions of hemocomponents (whole blood, red blood cells, plasma, platelets) (see Table 5, [98]).

Moreover, the severity of bleeding or the need for urgent surgery or other invasive procedures requires urgent reversal of the anticoagulant effect that consists of different strategies depending on the anticoagulant drug used [97, 98].

What to do if a patient taking VKAs bleeds?

In case of minor bleeding, it is recommended to identify any local causes of bleeding and to treat them (for example, epistaxis and gum bleeds can be treated with local antifibrinolytics). Furthermore, if the INR is in the therapeutic range, it is indicated to reduce the dose of the VKA until the complete resolution of bleeding. In the case of overdose, it is recommended to decrease INR to the therapeutic range by withdrawing VKA and administering vitamin K per os (2–3 mg) [99]. When VKA-treated patients present with major bleeding, in addition to the suspension of the anticoagulant treatment and general supportive measures, rapid reversal of anticoagulation is needed, particularly if the bleeding is life threatening. Guidelines recommend IV vitamin K administration at a dose of 10 mg [99]; it should be considered that vitamin K reduces INR values with a latency of several hours; therefore, it is given in combination with other drugs. For this purpose, several products are available to be used in emergency situations: prothrombin complex concentrates (PCCs) with 3 (II, IX, X) or 4 (II, VII, IX and X) factors, fresh frozen plasma (FFP), or recombinant activated factor VII (rFVIIa) [91]. FFP has the disadvantage of potential allergic reaction or transmission of infection, preparation time, and high injection volume. The use of rFVIIa in the reversal of major bleeding during VKA treatment has been described in case reports or a very few small studies and, to date, no randomized clinical trial has compared its efficacy and safety with that of PCCs or FFP in this setting. Regarding PCCs, no comparison trial between 3 and 4-factor preparations is available; however, it has been demonstrated that 3-factor PCCs are usually inadequate to

Table 5 General measures in case of bleeding during anticoagulant treatment (modified from Ref. [98])

Provide local haemostasis (ice, compression, suture, nasal packing, etc.)
Monitor hemodynamic status and blood losses
Provide hemodynamic support (vasopressors, fluid replacement)
Consider transfusions of red blood cells, fresh frozen plasma, platelets (if low platelet count or antiplatelet comedication)
Consider infusion of cryoprecipitate or fibrinogen concentrates, especially if fibrinogen < 1 g/L
Consider agents that may improve haemostasis: tranexamic acid, desmopressin
Plan radiological interventions, endoscopy or surgery after restoration of hemostasis is achieved

ensure rapid anticoagulation reversal when INR values are very high [100].

Therefore, national (FCSA, [99]) and international (ACCP [59]) guidelines agree in recommending the 4-factor PCCs as a first-choice treatment, in addition to vitamin K administration, in the setting of VKA-associated major bleeding (Table 6). Finally, the use of anti-fibrinolytic agents (e.g., tranexamic acid, 1 g IV every 6 h, if needed) or desmopressin 0.3 µg/kg IV infusion (with a maximal dosing of 20 µg) may be considered in special situations, such as in trauma-induced bleeding [99].

What to do if a patient taking DOACs bleeds?

The prescribed DOACs regimen, time of last dose intake, any co-medications and renal function is critical information in this setting [97]. Given the short half-life of DOACs, most bleeding complications—mainly minor or clinically relevant nonmajor—can be safely managed by only delaying intake or withholding the DOAC administration for a maximum of one dose [91]. In patients with major bleeding, reverse strategies will be used in case of:

(a) last DOAC intake in the last 12 h,
(b) last DOAC intake in the last 24–48 h in the presence of renal failure (and up to 96 h in patients taking dabigatran or in patients with severe renal failure, i.e., creatinine clearance < 30 mL/min),
(c) persistent bleeding,
(d) life-threatening bleeding (intracranial or in critical site) [97].

In case of last DOAC intake within the last 2 h, the administration of active charcoal can be useful; dialysis is effective only to clear dabigatran from plasma thanks to the low affinity for plasma proteins of this drug; [97].

As for hemostatic agents, their use should be considered in case of life-threatening bleeding if immediate hemostatic support is required, especially in situations where a specific reversal agent is not available [91]. Even in the absence of conclusive evidence, 4-factors PCCs are preferred over 3-factors PCCs at a suggested dose of 25–50 UI/kg [91, 97]. Regarding activated PCC concentrates (aPCC-FEIBA), these agents may be considered, at a dose of 50 UI/kg, for DOAC reversal only in patients with persistent life-threatening bleeding, due to the increased thrombotic risk associated with their administration [91]. On the contrary, because no efficacy studies are currently available, there is no role for FFP and rFVIIa in the reversal of DOACs. Finally, although suggested by EHRA guidelines, the use of tranexamic acid is controversial [97].

Specific antidotes, with rapid (few minutes) neutralization of the pharmacological effect of DOACs, have been successfully tested in Phase 3 clinical trials. These are idarucizumab for dabigatran and alpha for anti-Xa agents [101, 102].

Idarucizumab is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its acylglucuronide metabolites with higher affinity (350 folds) than the binding affinity of dabigatran to thrombin and, thereby, neutralizes dabigatran and its metabolites anticoagulant effect. Its use has been approved by FDA and EMA, and it is now available for clinical use. The recommended dose of idarucizumab is 5 g, administered IV in two separate doses by 2.5 g each, overall diluted in 100 mL of solvent [97, 101]. Andexanet alfa is a human recombinant FXa, created for the specific reversal of both direct and indirect FXa inhibitors. Phase I and phase II studies find a bolus followed by 2-h IV infusion to be the most suitable modality of andexanet administration to restore a sustained hemostasis [102]. Recently, in light of the interim results of the ANNEXA-4 study, this antidote has been approved by FDA (EMA approval is expected in the next months) for the reversal of the anticoagulant effect of rivaroxaban and apixaban, but not of edoxaban. Another antidote with more generalized antagonistic effects, Ciraparantag (Arapazine, PER 977), is now undergoing clinical testing [103].

According to a recent ISTH statement [104], the indications for the use of the antidotes are:

- life-threatening bleeding: intracranial or uncontrollable bleeding with the usual measures;
- bleeding in an enclosed space or in a critical organ;
- persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding due to delayed clearance or overdose of DOACs;
- emergency interventional procedures, surgery or surgery in patients at high risk of procedural bleeding: neurosurgery, lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), liver or other major surgery.

Table 7 shows a potential useful approach to DOAC-associated major bleeding.

Table 6 Reversal strategies to VKA-associated major bleeding (modified from Ref. [99])

VKA suspension, vitamin K administration (10 mg intravenously in at least 30 min) AND:	
INR 1.5–2	PCC 20 UI/kg body weight[a]
INR 2.1-3.9	PCC 30 UI/kg body weight[a]
INR 4.0–5.9	PCC 40 UI/kg body weight[a]
INR > 6	PCC 50 UI/kg body weight[a]
After PCC administration, check INR: if > 1.5, repeat PCC infusion	

[a]PCC (4 factors) is given intravenously in 15–20 min

What to do if a patient taking parenteral anticoagulants (UFH, LMWH and fondaparinux) bleeds?

In case of UFH administration, its short half-life (ranging between 60 and 90 min), ensures that non-life-threatening bleedings can be managed by simply discontinuing the drug (in addition to general supportive measures if needed). If the bleeding is life-threatening or not adequately controlled, IV administration of protamine sulfate is recommended [98]. 1 mg of protamine sulfate neutralizes roughly 100 U of UFH; considering the half-life of IV UFH, the protamine dose is calculated on UFH units infused over the last 2 h, with a maximum dose of 50 mg. If UFH is given SC, its neutralization may be achieved by a prolonged protamine infusion [98]. During protamine administration, aPTT monitoring is required to confirm the efficacy of reversal; moreover, due to the documented possible adverse reactions (such as bradycardia or arterial hypotension), a slow infusion of protamine sulfate is recommended [98]. For patients with LMWH-induced bleeding who require urgent reversal, there is no proven method to neutralize the drug. Protamine sulfate indeed only partially binds LMWH (about 30–40%). Moreover, while completely neutralizing the thrombin-inhibitory activity of LMWH, it only partially neutralizes the anti-FXa activity. The suggested dose of protamine is 1 mg every 100 U of LMWH given in the last 8 h [98]. Regarding fondaparinux, no specific antidote exists for its reversal; in case of major refractory bleeding while taking this drug, rFVIIa, at a dose ranging from 20 and 120 mcg/kg body weight, may be effective [98, 105]. It should be noted that the above-mentioned andexanet alfa [102] and cirapantag [103], which are still under testing, might have a role in antagonizing the effect of all parenteral anticoagulants.

Table 8 shows the suggested reversal measures for the management of major and life-threatening bleeding during treatment with parenteral anticoagulants [98].

Key points

- Minor bleedings can be managed without interruption, or with minimal variation of the anticoagulant treatment (i.e., reducing, delaying or skipping one dose of the drug). In all cases of major bleeding, and in almost all cases of CRNMB, the discontinuation of anticoagulant therapy is needed.
- When VKA-treated patients present with major bleeding, in addition to the suspension of the anticoagulant treatment and supportive measures, IV vitamin K and IV PCCs are recommended.
- For major bleedings during dabigatran treatment, idarucizumab should be administered whereas for those during anti-Xa agents 4-factors PCCs or aPCC should be considered.
- In case of UFH treatment, its short half-life ensures that non-life-threatening bleedings can be managed by simply discontinuing the drug, in addition to supportive measures. If the bleeding is life threatening or not adequately controlled, the IV administration of protamine sulfate is recommended. Protamine sulfate may only partially bind LMWH (about 30–40%); moreover, it completely neutralizes the thrombin-inhibitory activity of LMWH, but only partially neutralizes the anti-FXa activity. Regarding fondaparinux, no specific antidote exists for its reversal; in case of major refractory bleeding while being treated with this drug, rFVIIa may be effective.

Table 7 Suggested approach to DOAC-associated major bleeding (modified from Ref. [91])

	Direct thrombin inhibitor (dabigatran)	FXa inhibitors (rivaroxaban, apixaban, edoxaban)
No life-threatening major bleeding	General supportive measures Tranexamic acid can be considered as adjuvant (1 g i.v., repeat every 6 h, if necessary) Desmopressin can be considered in special cases such as coagulopathy or thrombocytopathy; 0.3 mg/kg i.v. infusion (max dose 20 μg) Only for dabigatran: Maintain diuresis Consider dialysis Consider idarucizumab (see below)	
Life-threatening major bleeding	All the above Direct reversal: Idarucizumab 5 g i.v. in two doses a 2.5 g i.v. no more than 15 min apart	All the above Direct reversal: Andexanet alpha (if available and approved by EMA)
Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) Activated PCC (aPCC) 50 U/kg; max 200 U/kg/day: no strong data about additional benefit over PCC. Can be considered before PCC, if available[a]		

[a]It induces a strong pro-coagulant effect and should be used by experienced physicians

Table 8 Reversal measures for major and life-threatening bleeding during treatment with parenteral anticoagulants (modified from Ref. [98])

Drug	Reversal strategies
UFH	Protamine sulfate: 1 mg/100 U of UFH given in the preceding 2 h
LMWH	Protamine sulfate: 1 mg/100 U of LMWH given in the preceding 8 h
Fondaparinux	No antidote Consider off-label rFVIIa in critical bleeding

Conclusion and perspectives

In cancer patients, VTE events can significantly increase morbidity and mortality as well as provide an impact on essential anti-cancer treatments. Therefore, primary prevention and the correct treatment of VTE are priorities in the management of these patients.

Primary VTE prophylaxis in hospitalized cancer patients and during and after cancer surgery is substantially well defined, but the evidence is less clear in ambulatory cancer patients receiving anti-cancer treatments. The risk variability between these patients, determined by several factors including cancer type and patient's characteristics, has led to efforts to stratify patients at high or low risk of events, with the development of assessment models to guide prescription of prophylaxis.

In cancer patients affected by VTE, the therapy of choice has been LMWH for a long time. However, the analysis of subgroups of cancer patients in trials with DOACs has already demonstrated efficacy and safety that might be similar to patients without cancer. Two recent trials have shown a good performance of DOACs versus dalteparin, suggesting that these drugs are at least as effective as LMWH in the prevention of recurrences of VTE. With the exception of gastrointestinal malignancies, the risk/benefit tradeoffs of DOACs are presently well defined. Further information on different risk/benefit ratio of different DOACs and on risk factors for bleeding during DOACs treatment is likely to emerge from ongoing trials and to strengthen the results of the recently published studies.

Compliance with ethical standards

Conflict of interest DP declares fees for participations in editorial boards and lectures by Bayer, Boehringer Ingelheim, BMS-Pfizer and Daiichi Sankyo given to his Institution. PP declares speakers' fees by Bayer, Boehringer Ingelheim, BMS-Pfizer and Daiichi Sankyo. FP declares fees for lectures by Bayer, Boehringer Ingelheim, BMS-Pfizer and Daiichi Sankyo. AT, CC, FS, GDM declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any study with human and animals performed by any of the authors.

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References

1. Falanga A, Russo L, Milesi V, Vignoli A (2017) Mechanisms and risk factors of thrombosis in cancer. Crit Rev Oncol Hematol 118:79–83
2. Farge D, Bounameaux H, Brenner B et al (2016) International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 17:e452–e466
3. Donnellan E, Khorana AA (2017) Cancer and venous thromboembolic disease: a review. Oncologist 22:199–207
4. Khorana AA, Carrier M, Garcia DA, Lee AYY (2016) Guidance for the prevention and treatment of cancer-associated venous thromboembolism. J Thromb Thrombolysis 41:81–91
5. Prandoni P, Lensing AW, Piccioli A et al (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 100:3484–3488
6. Connolly GC, Francis CW (2013) Cancer-associated thrombosis. Hematol Am Soc Hematol Educ Prog 2013:684–691
7. Mukai M, Oka T (2018) Mechanism and management of cancer-associated thrombosis. J Cardiol 72:89–93
8. Eichinger S (2016) Cancer associated thrombosis: risk factors and outcomes. Thromb Res 140:S12–S17
9. Laporte S, Mismetti P, Decousus H, RIETE Investigators et al (2008) Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad Trombo Embolica venosa (RIETE) Registry. Circulation 117:1711–1716
10. Donadini MP, Ageno W (2011) Unusual site thrombosis. Semin Hematol 48:264–270
11. Tufano A, Ageno W, Di Micco P et al (2018) Outcomes during anticoagulation in patients with symptomatic vs. incidental splanchnic vein thrombosis. Thromb Res 164:69–74
12. Khorana AA (2012) Cancer-associated thrombosis: updates and controversies. Hematol Am Soc Hematol Educ Program 2012:626–630
13. Menapace LA, Peterson DR, Berry A et al (2011) Symptomatic and incidental thromboembolism are both associated with mortality in pancreatic cancer. Thromb Haemost 106:371–378
14. Prisco D, D'Elios MM, Cenci C, Ciucciarelli L, Tamburini C (2014) Cardiovascular oncology: a new discipline inside internal medicine? Intern Emerg Med 9:359–364
15. Falanga A, Panova-Noeva M, Russo L (2009) Procoagulant mechanisms in tumor cells. Best Pract Res Clin Haematol 22:49–60
16. Khorana AA, Connolly GC (2009) Assessing risk of venous thromboembolism in the patient with cancer. J Clin Oncol 27:4839–4847
17. Chew HK, Davies AM, Wun T et al (2008) The incidence of venous thromboembolism among patients with primary lung cancer. J Thromb Haemost 6:601–608

18. Lyman GH, Bohlke K, Khorana AA et al (2015) Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol 33:654–656
19. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111:4902–4907
20. Khorana AA, McCrae KR (2014) Risk stratification strategies for cancer-associated thrombosis: an update. Thromb Res 133(Suppl 2):S35–S38
21. Ay C, Dunkler D, Marosi C et al (2010) Prediction of venous thromboembolism in cancer patients. Blood 116:5377–5382
22. Khorana AA, Francis CW (2018) Risk prediction of cancer-associated thrombosis: appraising the first decade and developing the future. Thromb Res 164:S70–S76
23. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R (2012) A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the PROTECHT score. Intern Emerg Med 7:291–292
24. Cella CA, Di Minno G, Carlomagno C et al (2017) Preventing venous thromboembolism in ambulatory cancer patients: the ONKOTEV study. Oncologist 22:601–608
25. Gerotziafas GT, Taher A, Abdel-Razeq H et al (2017) A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS-cancer-associated thrombosis study. Oncologist 22:1222–1231
26. Palumbo A, Rajkumar SV, Dimopoulos MA et al (2008) Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 22:414–423
27. Den Exter PL, Kooiman J, Huisman MV (2013) Validation of the Ottawa prognostic score for the prediction of recurrent venous thromboembolism in patients with cancer-associated thrombosis. J Thromb Haemost 11:998–1000
28. Lyman GH, Culakova E, Poniewierski MS, Kuderer NM (2018) Morbidity, mortality and costs associated with venous thromboembolism in hospitalized patients with cancer. Thromb Res 164(Suppl 1):S112–S118
29. Samama MM, Cohen AT, Darmon JY et al (1999) A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients.Prophylaxis in medical patients with enoxaparin study group. N Engl J Med 341:793–800
30. Leizorovicz A, Cohen AT, Turpie AG et al (2004) Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 110:874–879
31. Cohen AT, Davidson BL, Gallus AS et al (2006) Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 332:325–329
32. Streiff MB, Holmstrom B, Ashrani A et al (2015) Cancer-associated venous thromboembolic disease, version 1.2015. J Natl Compr Canc Netw 13:1079–1095
33. Mandala M, Falanga A, Roila F (2011) Management of venous thromboembolism [VTE] in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 22(Suppl 6):vi85–vi92
34. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, Le H, Schulman S, Murad MH (2012) Prevention of VTE in nonsurgical patients: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e195S–e226S
35. Barbar S, Noventa F, Rossetto V et al (2010) A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 8:2450–2457
36. Di Nisio M, Carrier M, Lyman GH et al (2014) Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost 12:1746–1749
37. Carrier M, Khorana AA, Moretto P, La Gal G, Karp R, Zwicker JI (2014) Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. Am J Med 127:82–86
38. Patell R, Rybicki L, McCrae KR, Khorana AA (2017) Predicting risk of venous thromboembolism in hospitalized cancer patients: utility of a risk assessment tool. Am J Hematol 92:501–507
39. Hull RD, Schellong SM, Tapson VF, for the EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study et al (2010) Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med 153:8–18
40. Goldhaber SZ, Leizorovicz A, Kakkar AK, for the ADOPT Trial Investigators et al (2011) Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med 365:2167–2177
41. Cohen AT, Spiro TE, Buller HR, for the MAGELLAN Investigators et al (2013) Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med 368:513–523
42. Bergqvist D, Agnelli G, Cohen AT et al (2002) Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 346:975–980
43. Rasmussen MS, Jorgensen LN, Wille-Jørgensen P et al (2006) Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicentre randomized open-label study. J Thromb Haemost 4:2384–2390
44. Guo Q, Huang B, Zhao J et al (2017) Perioperative pharmacological thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. Ann Surg 265:1087–1093
45. Fagarasanu A, Alotaibi GS, Hrimiuc R, Lee AY, Wu C (2016) Role of extended thromboprophylaxis after abdominal and pelvic surgery in cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 23:1422–1430
46. Gould MKI, Garcia DA, Wren SM et al (2012) Prevention of VTE in nonorthopedic surgical patients. antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e227S–e277S
47. Agnelli G, George DJ, Kakkar AK, SAVE-ONCO Investigators et al (2012) Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 366:601–609
48. Maraveyas A, Waters J, Roy R et al (2012) Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 48:1283–1292
49. Riess H, Pelzer U, Hilbig A et al (2008) Rationale and design of PROSPECT-CONKO 004: a prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy). BMC Cancer 8:361
50. Khorana AA, Vadhan-Raj S, Kuderer NM et al (2017) Rivaroxaban for preventing venous thromboembolism in high-risk ambulatory patients with cancer: rationale and design of the CASSINI Trial. Thromb Haemost 117:2135–2145
51. Kimpton M, Wells PS, Carrier M (2018) Apixaban for the prevention of venous thromboembolism in high-risk ambulatory cancer patients receiving chemotherapy: rational and design of the AVERT trial. Thromb Res 164(Suppl 1):S124–S129
52. Hakoum MB, Kahale LA, Tsolakian IG et al (2018) Anticoagulation for the initial treatment of venous thromboembolism in people with cancer. Cochrane Datab Syst Rev 1:CD006649
53. van Doormaal FF, Raskob GE, Davidson BL et al (2009) Treatment of venous thromboembolism in patients with cancer:

subgroup analysis of the Matisse clinical trials. Thromb Haemost 101:762–769
54. Wells PS, Anderson DR, Rodger MA et al (2005) A randomized trial comparing 2 low molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Arch Intern Med 165:733–738
55. Othieno R, Abu Affan M, Okpo E (2007) Home versus in-patient treatment for deep vein thrombosis. Cochrane Datab Syst Rev 3:CD003076
56. Lee AY, Levine MN, Baker RI et al (2003) Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349:146–153
57. Meyer G, Marjanovic Z, Valcke J et al (2002) Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 162:1729–1735
58. Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA (2015) CATCH Investigators. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA 314:677–686
59. Kearon C, Akl EA, Ornelas J et al (2016) Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 149:315–352
60. NCCN Guidelines (2017) Cancer-associated venous thromboembolism. Version-I. https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf
61. Khorana AA, Yannicelli D, McCrae KR, Milentijevic D, Crivera C, Nelson WW, Schein JR (2016) Evaluation of US prescription patterns: are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 145:51–53
62. Imberti D, Cimminiello C, Di Nisio M et al (2018) Antithrombotic therapy for venous thromboembolism in patients with cancer: expert guidance. Expert Opin Pharmacother 19:1177–1185
63. Posch F, Königsbrügge O, Zielinski C, Pabinger I, Ay C (2015) Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res 136:582–589
64. Brunetti ND, Gesuete E, De Gennaro L et al (2017) Direct oral anti-coagulants compared with vitamin-K inhibitors and low-molecular-weight-heparin for the prevention of venous thromboembolism in patients with cancer: a meta-analysis study. Int J Cardiol 230:214–221
65. Hulle T, Exter P, Kooiman J, Hoeven J, Huisman M, Klok F (2014) Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. J Thromb Haemost 12:1116–1120
66. Vedovati MC, Germini F, Agnelli G, Becattini C (2015) Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest 147:475–483
67. Raskob GE, van Es N, Verhamme P, Hokusai VTE Cancer Investigators et al (2018) Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 378:615–624
68. Young AM, Marshall A, Thirlwall J et al (2018) Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 36:2017–2023
69. Li A, Garcia DA, Lyman GH, Carrier M (2018) Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. Thromb Res. https://doi.org/10.1016/j.thromres.2018.02.144
70. Lee AYY (2018) Overview of VTE treatment in cancer according to clinical guidelines. Thromb Res 164:S162–S167
71. Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, Carrier M (2018) Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 16:1891–1894
72. Lee AYY (2017) When can we stop anticoagulation in patients with cancer-associated thrombosis? Blood. https://doi.org/10.1182/blood-2017-05-787929
73. Lee AYY (2017) When can we stop anticoagulation in patients with cancer-associated thrombosis? Hematol Am Soc Hematol Educ Prog 2017:128–135
74. Menapace LA, McCrae KR, Khorana AA (2016) Predictors of recurrent venous thromboembolism and bleeding on anticoagulation. Thromb Res 140(Suppl 1):S93–S98
75. Chee CE, Ashrani AA, Marks RS, Petterson TM, Bailey KR, Melton LJ 3rd, Heit JA (2014) Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. Blood 123:3972–3978
76. Francis CW, Kessler CM, Goldhaber SZ et al (2015) Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 13:1028–1035
77. Jara-Palomares L, Solier-Lopez A, Elias-HernandezLuis T et al (2017) Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study. Thromb Res 157:90–96
78. Prandoni P (2017) The treatment of venous thromboembolism in patients with cancer. Adv Exp Med Biol 906:123–135
79. Carrier M, Khorana A, Zwicker J, Noble S, Lee A (2013) Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH. J Thromb Haemost 11:1760–1765
80. Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY (2009) Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost 7:760–765
81. Piran S, Schulman S (2018) Management of recurrent venous thromboembolism in patients with cancer: a review. Thromb Res 164(Suppl 1):S172–S177
82. Singh R, Sousou T, Mohile S, Khorana AA (2010) High rates of symptomatic and incidental thromboembolic events in gastrointestinal cancer patients. J Thromb Haemost 8:1879–1881
83. Connolly GC, Menapace L, Safadjou S, Francis CW, Khorana AA (2013) Prevalence and clinical significance of incidental and clinically suspected venous thromboembolism in lung cancer patients. Clin Lung Cancer 14:713–718
84. Chaturvedi S, Sidana S, Elson P, Khorana AA, McCrae KR (2014) Symptomatic and incidental venous thromboembolic disease are both associated with mortality in patients with prostate cancer. PLoS One 9:e94048
85. den Exter PL, Hooijer J, Dekkers OM, Huisman MV (2011) Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. J Clin Oncol 29:2405–2409
86. Carrier M, Righini M, Le Gal G (2012) Symptomatic subsegmental pulmonary embolism: what is the next step? J Thromb Haemost 10:1486–1490
87. Investigators Hokusai-VTE, Büller HR, Décousus H, Grosso MA et al (2013) Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 369:1406–1415
88. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP (2018) Oral anticoagulation in patients with liver disease. J Am Coll Cardiol 71:2162–2175

89. Pastori D, Lip GYH, Farcomeni A, ATHERO-AF study group et al (2018) Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants. Int J Cardiol 264:58–63
90. Short NJ, Connors JM (2014) New oral anticoagulants and the cancer patient. Oncologist 19:82–93
91. Steffel J, Verhamme P, Potpara TS et al (2018) The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 39:1330–1393
92. Khanal N, Bociek RG, Chen B, Vose JM, Armitage JO, Bierman PJ, Maness LJ, Lunning MA, Gundabolu K, Bhatt VR (2016) Venous thromboembolism in patients with hematologic malignancy and thrombocytopenia. Am J Hematol 91:E468–E472
93. Samuelson Bannow BT, Lee A, Khorana AA, Zwicker JI, Noble S, Ay C, Carrier M (2018) Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. J Thromb Haemost 16:1246–1249
94. Kopolovic I, Lee AY, Wu C (2015) Management and outcomes of cancer-associated venous thromboembolism in patients with concomitant thrombocytopenia: a retrospective cohort study. Ann Hematol 94:329–336
95. Campbell PM, Ippoliti C, Parmar S (2017) Safety of anticoagulation in thrombocytopenic patients with hematologic malignancies: a case series. J Oncol Pharm Pract 23:220–225
96. van der Wall SJ, Klok FA, den Exter PL et al (2017) Continuation of low-molecular-weight heparin treatment for cancer-related venous thromboembolism: a prospective cohort study in daily clinical practice. J Thromb Haemost 15:74–79
97. Prisco D, Ageno W, Becattini C et al (2017) Italian intersociety consensus on DOAC use in internal medicine. Intern Emerg Med 12:387–406
98. Sartori MT, Prandoni P (2016) How to effectively manage the event of bleeding complications when using anticoagulants. Expert Rev Hematol 9:37–50
99. Federazione Centri per la Diagnosi della Trombosi e Sorveglianza delle Terapie Antitrombotiche (FCSA) (2012) Guida alla terapia con anticoagulanti orali. Raccomandazioni. XI Edizione
100. Makris M, van Veen JJ (2011) Three or four factor prothrombin complex concentrate for emergency anticoagulation reversal? Blood Transfus 9:117–119
101. Pollack CV Jr, Reilly PA, Eikelboom J et al (2015) Idarucizumab for dabigatran reversal. N Engl J Med 373:511–520
102. Connolly SJ, Milling TJ Jr, Eikelboom JW et al (2015) Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 375:1131–1141
103. Ansell JE, Bakhru SH, Laulicht BE et al (2014) Use of PER977 to reverse the anticoagulant effect of edoxaban. N Engl J Med 371:2141–2142
104. Levy JH, Ageno W, Chan NC et al (2016) When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost 14:623–627
105. Elmer J, Wittels KA (2012) Emergency reversal of pentasaccharide anticoagulants: a systematic review of the literature. Transfus Med 22:108–115