Cancer-associated venous thromboembolism: Burden, mechanisms, and management

Cihan Ay[1]; Ingrid Pabinger[1]; Alexander T. Cohen[2]

[1]Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria; [2]Department of Haematological Medicine, Guy's and St Thomas' Hospitals, King's College London, London, United Kingdom

Summary

Venous thromboembolism (VTE) is a significant health problem in the general population but especially in cancer patients. In this review, we discuss the epidemiology and burden of the disease, the pathophysiology of cancer-associated VTE, and the clinical treatment options for both primary prevention and acute treatment. Overall, the development of VTE in cancer patients is related to increases in morbidity, mortality, and medical costs. However, the incidence of cancer-associated VTE varies due to patient-related factors (e.g. thrombophilia, comorbidities, performance status, history of venous diseases), tumour-related factors (e.g. cancer site, stage, grade), and treatment-related factors (e.g. surgery, chemotherapy, anti-angiogenesis treatment, hormonal and supportive treatment). Furthermore, blood count parameters (e.g. platelets and leukocytes) and biomarkers (e.g. soluble P-selectin and D-dimer) are predictive markers for the risk of VTE in cancer patients and have been used to enhance risk stratification. Evidence suggests that cancer itself is associated with a state of hypercoagulability, driven in part by the release of procoagulant factors, such as tissue factor, from malignant tissue as well as by inflammation-driven activation of endothelial cells, platelets, and leukocytes. In general, low-molecular-weight heparin (LWMH) monotherapy is the standard of care for the management of cancer-associated VTE, as vitamin K antagonists are less effective in cancer patients. Direct oral anticoagulants (DOACs) offer a potentially promising treatment option for cancer patients with VTE, but recommendations concerning the routine use of DOACs should await head-to-head studies with LMWH.

Keywords

Venous thromboembolism, cancer, epidemiology, risk factors, treatment

Correspondence to:
Dr. Cihan Ay, MD
Medical University of Vienna, Department of Medicine I,
Clinical Division of Haematology and Haemostaseology
Waehringer Guertel 18–20, A-1090 Vienna, Austria
Tel.: +43 1 40400 44100, Fax: +43 1 40400 40300
E-mail: cihan.ay@meduniwien.ac.at

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Introduction

Venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a significant health problem with an estimated annual incidence of approximately 1 to 2 per 1,000 people among the general population (1). However, the prevalence, morbidity, and mortality associated with VTE are especially elevated among cancer patients. The estimated risk of developing VTE is approximately 4- to 6.5-fold higher in cancer patients compared with patients without cancer (2, 3). In addition, among cancer patients, VTE is one of the leading causes of death (4). From this, it has been hypothesised that malignancy induces a hypercoagulable state in cancer patients (5).

The association between cancer and VTE was first clinically identified in the 1800s when Jean-Baptiste Bouillaud and subsequently Armand Trousseau described the relationship (6). At that time, Trousseau noted that spontaneous coagulation is common in cancer patients (7). Trousseau was so confident of this association that he presciently diagnosed his own malignancy based on thrombophlebitis in his upper extremity (8). Subsequent research has improved our understanding of the relationship between cancer and VTE. Here we review the epidemiology and burden of the disease, the pathophysiology of cancer-associated VTE, and the clinical treatment options for both primary prevention and acute treatment.

Epidemiology and burden

Cancer is a strong and independent risk factor for VTE (2, 3). Overall, cancer accounts for an estimated 18 % (95 % confidence interval [CI]: 13.4 % to 22.6 %) of the total number of VTE cases (9). Based on hospitalisation rates for VTE, the incidence rate for cancer-associated VTE was estimated to be 8 patients per 1000 patients/year (10). Similarly, in the Vienna Cancer and Thrombosis Study (CATS)–a large, prospective observational study–the cumulative incidence of VTE among cancer patients over the median observation time of approximately 19 months was 7.4 % (11).

In a large registry study, cancer was found to be the strongest independent risk factor for all-cause and PE-related mortality in patients with VTE (12). In that study, 3% of deaths in cancer patients were PE-related versus 1% of deaths in noncancer patients (p <0.001) (12). Overall, survival rates are significantly lower and prognosis significantly worse in cancer patients with VTE relative to those without (13–16). For instance, in a Danish registry study, patients with cancer diagnosed concurrently with VTE had a significantly lower one-year survival rate (12% vs 36%; p <0.001) and significantly more distant metastases (prevalence ratio [95% CI]: 1.26 [1.13 to 1.40]) compared with cancer patients without VTE (15).

In addition to the increased risk of VTE in cancer patients and the worse prognosis linked to cancer-associated VTE, healthcare costs are approximately 40% to 50% higher in cancer patients with VTE as compared with cancer patients without VTE (17–19). In a population-based, longitudinal cohort study, after adjusting for cofactors including age, sex, and cancer type and stage, the direct five-year healthcare costs were significantly higher in cancer patients with VTE versus cancer patients without VTE (approximately $49,000 vs $27,000 in 2013 US dollars; p ≤0.001) (20). These increased healthcare costs in VTE cancer patients are primarily driven by higher inpatient and outpatient costs (19, 20).

Risk factors and biomarkers

Risk factors for developing VTE in cancer patients can be grouped into tumour-related factors, patient-related factors, treatment-related factors, and biomarkers (►Figure 1). A better understanding of clinical risk factors and biomarkers can help with determining an individual cancer patient's risk for VTE.

Tumour-related risk factors

Tumour-related factors include the primary site, grade, and cancer stage, as well as the time since diagnosis. In a 1989 study investigating the prevalence of PE in cancer patients at autopsy, significantly more patients with cancer had PE on autopsy relative to noncancer patients dying of other causes, primarily of cardiovascular disease (10.5% vs 8.4%). The highest prevalence was reported for patients with ovarian cancer, cancer of the extrahepatic bile duct system, and cancer of the stomach (34.5%, 31.7%, and 15.2%, respectively) (21). Similarly, a 2006 large registry study assessing 20 of the most common cancers reported the highest incidence of concurrently diagnosed VTE in patients with metastatic cancers of the pancreas, stomach, lung, uterus, bladder, and kidney (13). In general, the types of cancer most often associated with

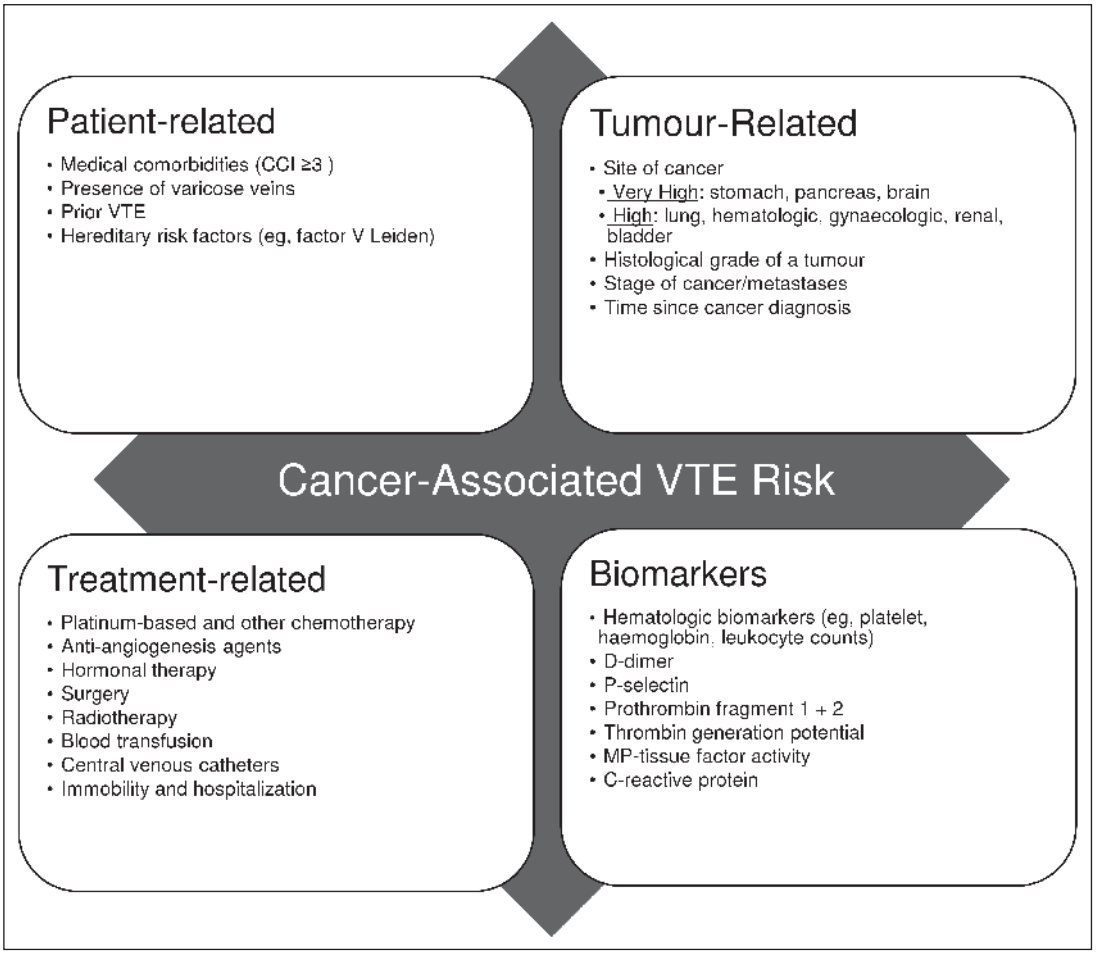

Figure 1: Risk factors for developing VTE in cancer patients grouped into tumour-related factors, patient-related factors, treatment-related factors, and the presence of biomarkers. CCI = Charleston Comorbidity Index; VTE = venous thromboembolism.

VTE are gastric and pancreatic cancers (2, 10, 13, 21–28). Other cancers associated with a high risk of VTE include brain, gynecological cancers, lung, renal, bladder, bone, and haematological malignancies (2, 10, 13, 18, 21–30).

Patients with metastatic cancers are at a significantly increased risk of developing VTE relative to patients with localised cancer (13, 14, 16, 24, 29). In CATS, the cumulative probabilities of VTE after six months in cancer patients with local, regional, or distant stage cancer, respectively, were 2.1%, 6.5%, and 6.0% (p = 0.002) (31). It is interesting to note that, in this study, the cumulative probability was similar in patients with regional or distant stage cancers while patients with local stage cancer had a much lower VTE risk (31).

The histological grading is also an important risk marker. In CATS, after adjusting for cofactors including distant metastases, sex, and age, the rate of VTE was approximately twice as high in patients with high-grade tumours compared with those with low-grade tumours (hazard ratio [HR] [95% CI], 2.0 [1.1–3.5]; p =0.015) (32). There is also an observed time-dependent association between VTE and cancer, with most VTE events occurring within the first 3-6 months after cancer diagnosis (2, 13, 14, 16, 18, 23, 29).

Patient-related risk factors

Patient-related factors associated with VTE in cancer patients include advanced age (≥65), obesity, and the presence of medical comorbidities (2, 14, 16, 23, 24, 28). While not all studies have replicated the association between advanced age or obesity and the increased risk for VTE in cancer patients (13, 16, 18, 33–35), the presence of medical comorbidities, particularly a Charlson Comorbidity Index ≥3, has consistently been linked with cancer-associated VTE (14, 16, 18, 23, 24, 28). The occurrence of varicose veins and prior VTE has also been associated with VTE in cancer patients (33–35).

In a large registry study, a family history of VTE was identified as a risk factor for VTE in patients with several cancer types including testicular, breast, rectal, and stomach cancers (36). Overall, accumulating evidence suggests that hereditary thrombophilia is also an important risk factor for cancer-associated VTE. For instance, the results of some (29, 37–39), but not all studies (35), suggest an association between hereditary prothrombotic genetic risk factors (e.g. factor V Leiden) and cancer-associated VTE. In one study, the risk of VTE was approximately 2-fold higher in patients with active cancer and a factor V Leiden mutation compared with patients with active cancer but no factor V Leiden mutation (40). Similarly, in a prospective study of women with breast cancer undergoing adjuvant tamoxifen treatment, patients who developed VTE were significantly more likely to have a factor V Leiden mutation compared with patients without VTE (41).

Treatment-related risk factors

Cancer treatment itself can significantly increase the risk of VTE (3, 10, 22, 28). Among cancer treatments, platinum-based chemotherapies (e.g. cisplatin) and anti-angiogenesis treatments (e.g. bevacizumab) are frequently associated with VTE (18, 23, 34, 42–45). In meta-analyses of clinical trials, patients treated with cisplatin or bevacizumab therapy were at significantly higher risk for VTE relative to patients treated with non-cisplatin or non-bevacizumab therapies (relative risk [RR] [95% CI]: 1.67 [1.25–2.23] and 1.33 [1.13–1.56], respectively) (44, 45). Other treatments associated with VTE in cancer patients include thalidomide, hormonal therapy, erythropoiesis-stimulating agents, and red blood cell or platelet transfusions (18, 22, 23, 28, 46, 47). In addition, cancer surgery is associated with VTE and there is some evidence to suggest an association between radiation therapy and VTE in patients with cancer (10, 23, 48, 49).

Biomarkers

Among haematologic biomarkers, an elevated platelet count is strongly and independently associated with VTE in cancer patients (35, 50, 51), with one study reporting a 3.5-fold increased risk of VTE in patients with platelet count ≥443×10^9/l (50). Haematologic biomarkers also associated with an increased risk of VTE in cancer patients include elevated leukocyte counts and low haemoglobin levels (43, 51, 52).

Other biomarkers independently associated with the presence of VTE in cancer patients in CATS include elevated plasma levels of soluble P-selectin (sP-selectin), prothrombin fragment 1+2 (F1+2), and D-dimer, as well as increased thrombin generation potential (50, 53–55). In addition, patients with distant metastases have significantly higher sP-selectin, F1+2, and D-dimer levels as compared with patients with localised cancers (31). P-selectin, a cell adhesion molecule primarily found in endothelial cells and platelets, is thought to mediate the adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer cell growth/metastasis (56). F1+2 is considered a specific *in vivo* marker of thrombin generation (57) and D-dimer is the primary degradation product of cross-linked fibrin and reflects the global activation of the haemostatic and fibrinolytic system (58). In patients with colorectal cancer, the presence of preoperative D-dimer was associated with an increased risk of VTE during the year post-surgery relative to patients negative for D-dimer presurgery (HR [95% CI]: 6.53 [1.58–27.0]; p =0.009) (59). Another biomarker linked to an increased risk of cancer-associated VTE is C-reactive protein (CRP) (34), a marker of systemic inflammation (60). However, not all studies have replicated the association between CRP and cancer-associated VTE (61).

There are very few studies assessing the longitudinal changes in cancer-associated VTE biomarkers in cancer patients. A recent longitudinal study over six months in patients with colorectal, lung, pancreatic, or brain cancer reported that cancer patients who developed VTE showed significantly elevated haemostasis biomarker levels, including sP-selectin and D-dimer, during the entire 250-day observation period versus those patients who did not develop VTE (62). As there was no continuous increase in D-dimer levels before VTE occurrence (62), the added value of continuous

biomarker monitoring, rather than a single measurement, in improving VTE prediction and patient care is not clear.

Risk assessment models

Based on these aforementioned risk factors, models were developed to stratify VTE risk in cancer patients. One goal of these predictive models is to identify cancer patients at high risk for cancer-associated VTE who may benefit from primary prevention. The first such risk model developed by Khorana et al., used baseline clinical and laboratory variables, including the primary site of cancer (stratified as very high, high, and low risk), body mass index (BMI), and platelet, leukocyte, and haemoglobin levels to predict VTE in cancer patients receiving chemotherapy (51). The final validated model divided patients into three risk categories based on their score on the Khorana risk model (i.e. low [score 0], intermediate [score 1–2], and high [score ≥3]) (51). In the original validation of the model, the risk score had a good negative predictive value (NPV) of 98.5% in patients with low risk but a relatively poor positive predictive value (PPV) of 7.1% in patients with high risk (51). A subsequent expanded risk model–which includes sP-selectin and D-dimer levels–is more accurate, with an NPV of 99.0% in patients with the lowest score and a PPV of 42.9% in cancer patients with the highest risk scores (63). The drawback of this latter model is that assays to assess sP-selectin are not readily available in routine clinical practice. As the risk of VTE is not assessed in many cancer patients using these risk models, there is a clear need for improvement of risk stratification by more accurate and easier-to-apply risk models suitable for everyday clinical practice.

Mechanisms of thrombosis in cancer

The pathogenesis of cancer-associated VTE is multifactorial and likely involves multiple overlapping pathways. All aspects of Virchow's triad (i.e. venous stasis, hypercoagulability, and vessel wall injury) (64) may play a role in cancer-associated VTE, including increased immobility, chemotherapy- and surgery-induced endothelial damage, and a cancer-induced state of hypercoagulability. Some of the factors contributing to the cancer-induced state of hypercoagulability include direct coagulation pathway activation, induction of inflammatory responses, and inhibition of fibrinolytic activity. ►Figure 2 shows an overview of some of these pathways.

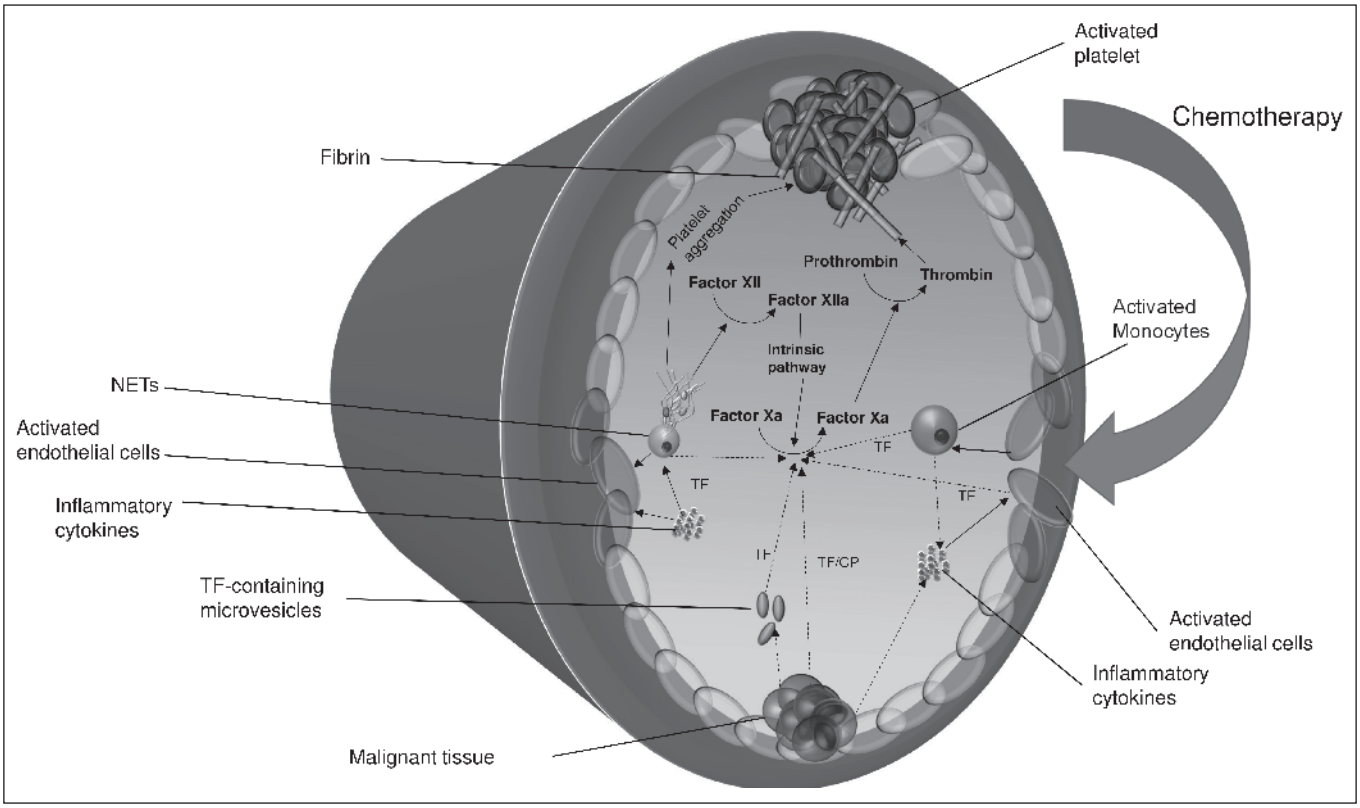

Figure 2: An overview of some of the pathways suggested to be involved in pathogenesis of cancer-associated venous thromboembolism. Malignant tumour cells can initiate the coagulation cascade through the release of procoagulant factors such as TF, microvesicles containing TF, and cancer procoagulant factor, as well as induce a hypercoagulable state through the induction of pro-inflammatory cytokines and the activation of monocytes and neutrophil granulocytes. In addition, cancer cells can inhibit fibrinolysis (not shown). Chemotherapy itself can create a hypercoagulable state through causing endothelial cell damage and through the induction of an inflammatory state. CP = cancer procoagulants; NETs = neutrophil extracellular traps; TF = tissue factor.

Direct coagulation pathway activation

Tumour cells themselves have been hypothesised to contribute to the hypercoagulable state through the production of procoagulant factors. For instance, a positive correlation was observed between serum concentration levels of cancer procoagulant (CP), a cysteine proteinase thought to be produced by tumour cells and a direct activator of coagulation factor X (65), and fibrinogen in patients with gastrointestinal adenocarcinomas (66).

Despite the presence of CP, the main mechanism by which cancer induces fibrin formation is suggested to be through an upregulation of tissue factor (TF) and through the production of TF-positive microvesicles. Tissue factor, a primary initiator of the coagulation cascade, is present in some cancer tissues, and patients with cancer often have elevated plasma TF concentration relative to individuals without cancer (67). In addition, in one study, TF expression in tumour cells was significantly correlated with the development of VTE in women with ovarian cancer (68). However, this finding was not confirmed in primary brain tumours (69).

Microvesicles are fragments shed from the plasma membrane of numerous cell types, including tumours, blood cells, and endothelial cells, when they are exposed to stress conditions and act as mediators of cell-to-cell communication (70). Microvesicles are often highly procoagulant; for instance, platelet-derived microvesicles have been reported to have 50– to 100-fold greater procoagulant activity than activated platelets (71). Compared with healthy adults, patients with cancer, including myeloma and metastatic breast and pancreatic cancers, have elevated TF-positive microvesicle activity (72–74), as do cancer patients with VTE compared with cancer patients without VTE (75). In cancer patients with high levels of TF-positive microvesicles, the cumulative incidence of VTE was 27% versus 7% in patients with low levels (76). In one study, a small but significant correlation was found between TF-positive microvesicle activity and time to fibrin clot formation in the plasma of patients with metastatic pancreatic cancer (74). Consistent with this finding, the presence of TF-positive microvesicle activity in cancer patients increased the risk of developing VTE 7-fold versus cancer patients without detectable levels (odds ratio [95% CI]: 7.00 [0.85–82.74]) (77). However, in an analysis of the CATS data, TF-positive microvesicle activity did not correlate with the risk of developing VTE in pancreatic, gastric, colorectal, or brain cancer patients when competing risk analysis was applied, but was associated with an increased risk of mortality in pancreatic cancer (78). While TF-positive microvesicles may originate from monocytes, in one study, 50% of circulating TF-positive microvesicles in patients with pancreatic cancer co-expressed MUC-1, a tumour marker for pancreatic cancer (77).

Other prothrombotic abnormalities observed in cancer patients may be related to the pathogenesis of cancer-associated VTE. For instance, an increase in von Willebrand factor and factor VIII and a reduction in protein S were reported in multiple myeloma patients (47, 79). In addition, prostate cancer cells express long chain polyphosphate on their surface, which one study showed can initiate coagulation through a factor XII-dependent manner (80).

Induction of inflammatory responses

Patients with cancer also have an increased level of circulating proinflammatory cytokines (81), which could contribute to abnormal fibrin clot formation. For instance, interleukin (IL)-6 can be significantly elevated in cancer patients with VTE compared with cancer patients without VTE and in cancer patients relative to healthy controls (75, 82). The release of proinflammatory cytokines such as IL-6 and tumour necrosis factor-alpha can alter the haemostatic balance by stimulating the release of procoagulant factors such as TF and von Willebrand factor from endothelial cells (83–85).

The inflammatory response to cancer or chemotherapy can also result in the formation of neutrophil extracellular traps (NETs), which are scaffolds of chromatin fibres lined with antimicrobial proteins (86). The formation of NETs (i.e. NETosis) was originally described as part of the innate immune system, in which the presence of pathogens can induce neutrophil granulocytes to release these extracellular traps that can capture and kill microbes (87). However, NETs are also found within DVTs and have prothrombotic effects (87, 88). In addition, tumours can secrete granulocyte colony stimulating factor, a cytokine that can contribute to cancer-associated thrombosis by systemically priming neutrophils toward NETosis (88).

In vitro co-localisation of neutrophils with activated endothelial cells (a proinflammatory and procoagulant state of endothelial cells associated with decreased vascular integrity and increased expression of leukocyte adhesion molecules (89)) results in NETosis, partly through the action of cytokines (90). NETs, in turn, promote fibrin formation through stimulating platelet adhesion and factor XII activation as well as inducing endothelial cell death (90–92).

Inhibition of fibrinolytic activity

In addition to the induction of fibrin clots, cancer can also result in an inhibition of fibrinolysis. Tumour cells can express plasminogen activator inhibitor-1 (PAI-1). PAI-1 is the major inhibitor of plasminogen activation by tissue-type plasminogen activator and therefore is an inhibitor of fibrin clot degradation (93). Elevated levels of PAI-1 were reported in individuals with different cancers, including ovarian cancer and multiple myeloma (82, 94). In addition, PAI-1 mRNA was detected in endothelial cells from the tumours of patients with colorectal cancer (95).

Clinical treatment considerations

The goal of anticoagulant treatment for VTE in cancer patients is the same as in other populations of patients at increased risk for VTE. In general, all of the treatment options for primary prevention and acute treatment of VTE are potentially also available for cancer patients with VTE (►Table 1). Vitamin K antagonists (VKAs) with initial heparinisation has long been considered a mainstay for the management of VTE (96). However, in cancer pa-

Table 1: Potential treatment options for cancer-associated VTE.

Class	Drugs for patients with VTE	Route of administration
VKA	Warfarin, Acenocoumarol, Phenprocoumon	Oral
Unfractionated heparin	Heparin	Parenteral
Low-molecular-weight heparin	Dalteparin, Enoxaparin, Tinzaparin, Nadroparin	Parenteral
Indirect factor Xa inhibitors	Fondaparinux	Parenteral
Direct oral anticoagulants		
Direct thrombin inhibitors	Dabigatran	Oral
Direct factor Xa inhibitors	Apixaban, Rivaroxaban, Edoxaban	Oral

VKA = vitamin K antagonist; VTE = venous thromboembolism.

tients, VKA treatment is associated with increased risk of recurrence and bleeding relative to patients without cancer (97–99). Cancer patients treated with VKA are at an approximately 3-fold higher risk of VTE recurrence and a 2- to 6-fold higher risk of bleeding (97, 98).

Guidelines for the treatment and prevention of cancer-associated VTE

Treatment guidelines, including from the American College of Chest Physicians, the American Society of Clinical Oncology (ASCO), the British Committee for Standards in Haematology (BCSH), the European Society of Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the International Clinical Practice Guidelines, recommend low-molecular-weight heparin (LMWH) for the short- and long-term management of VTE in cancer patients (►Table 2) (100–106). The International Clinical Practice Guidelines recommend that treatment should be continued 3 to 6 months, ASCO recommends continued treatment for at least six months, and the BCSH, NCCN and ESMO guidelines recommend anticoagulant therapy be continued indefinitely as long as there is clinical evidence of active malignant disease (101–106).

For the prevention of VTE in medical cancer patients in an inpatient setting or perioperatively, treatment guidelines recommend parenteral anticoagulants for pharmacologic thromboprophylaxis (►Table 2) (100–108). The International Clinical Practice Guidelines further specify that thromboprophylaxis should be initiated 2-12 hours preoperatively and continued for at least 7 to 10 days following surgery (104). After major cancer surgery (ab-

Table 2: Overview of current treatment guidelines for cancer-associated VTE.

Class (Ref.)	Prophylaxis	Acute treatment	Long-term treatment	Duration of extended treatment
ACCP (100)	–	For acute and long-term treatment (first 3 months), LMWH is preferred over VKA or DOACs in cancer patients In cancer patients not treated with LMWH, ACCP states no preference for VKAs or DOACs and no DOAC is preferred over the others	Extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy Continued use of treatment should be reassessed at periodic intervals	
ASCO (101, 105)	• Inpatient: Pharmacologic thromboprophylaxis recommended in the absence of bleeding or other contraindications • Perioperative: UFH or LMWH unless contraindicated because of active bleeding or high bleeding risk • Chemotherapy: LMWH in highly selected outpatients with solid tumours receiving chemotherapy; aspirin or LMWH (low-risk patients) and LMWH (high-risk patients) in multiple myeloma patients receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone	LMWH for the initial 5–10 days of anticoagulation for cancer patients with newly diagnosed VTE	LMWH (VKA is alternative when LMWH not available)	At least 6 months Select patients with active cancer (eg, metastatic disease or receiving chemotherapy) can continue beyond 6 months

Table 2: Continued.

Class (Ref.)	Prophylaxis	Acute treatment	Long-term treatment	Duration of extended treatment
BCSH (106)	• Inpatients: Thromboprophylaxis is recommended unless contraindicated • Outpatients: Outpatients with active cancer should be assessed for VTE risk and thromboprophylaxis considered for high-risk patients • Surgery: Patients undergoing abdominal and pelvic surgery for cancer should be considered for extended thromboprophylaxis • Chemotherapy: Patients with myeloma receiving thalidomide or lenalidomide should assessed for VTE risk and offered thromboprophylaxis unless contraindicated	LMWH for 6 months Warfarin or DOACs are an alternative for patients who cannot have or tolerate subcutaneous LMWH	LMWH Oral anticoagulant can be considered if the patient does not wish to continue with daily injections	In the presence of active malignancy, anticoagulation should be continued, taking patient status and wishes and bleeding risk into consideration
EMN (108)	• Chemotherapy: Patients at low risk for VTE starting immunomodulatory drugs for myeloma should take aspirin (100 mg); otherwise LMWH or full-dose warfarin should be used	Treatment of confirmed VTE has to be according to international or national guidelines	LMWH for ≥4 months and then patients may be switched to aspirin prophylaxis	
ESMO (102)	• Surgery: LMWH, UFH, or fondaparinux • Inpatients: UFH, LMWH, or • fondaparinux in hospitalized patients confined to bed • Chemotherapy: LMWH or warfarin in myeloma patients receiving thalidomide plus dexamethasone or thalidomide plus chemotherapy	LMWH	LMWH at 75 %–80 % of initial dose	For as long as there is clinical evidence of active malignant disease

dominal and pelvic cancer surgery) extended thromboprophylaxis after hospital discharge for approximately one month is recommended (101, 102, 105) because it was observed that in the post-discharge period, these patients frequently developed VTE (109). Thromboprophylaxis is not routinely recommended in ambulatory cancer patients undergoing chemotherapy (101–104). The Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis does not recommend thromboprophylaxis for outpatients with cancer deemed at low risk for VTE (107). However, in select populations of cancer patients with solid tumours or in myeloma patients receiving immunomodulatory agents, prophylaxis could be considered (primarily aspirin, VKA, or LWMH) (100–108). In patients with myeloma taking immunomodulatory agents, the European Myeloma Network recommends the LMWH prophylaxis can be continued for at least four months after which patients may be switched to aspirin (108).

Although the treatment guidelines differ slightly based on factors such as differences in treatment practices between nations and in how much weight is put on the available clinical trial data, there is a general consensus. Cancer-associated VTE should be treated for at least 3-6 months with a therapeutic dose of LMWH. In patients with complete remission, treatment can be stopped after six months. In patients with active cancer (e. g. presence of metastatic disease and/or ongoing anti-cancer treatment), treatment with LMWH at prophylactic doses or with oral anticoagulants, depending on patient preference, can be continued beyond six months.

Efficacy and safety of parenteral anticoagulants

The efficacy and safety of parenteral anticoagulants for the prevention and treatment of VTE in cancer patients have been investigated in numerous clinical trials and in secondary analyses, with generally favourable results (110–115). Overall, the results of a

Table 2: Continued.

Class (Ref.)	Prophylaxis	Acute treatment	Long-term treatment	Duration of extended treatment
International Clinical Practice Guidelines (104)[a]	• Inpatient: Prophylaxis with LMWH, UFH, or fondaparinux in hospitalized medical patients with cancer and reduced mobility • Surgery: The highest prophylactic dose of LMWH once a day or a low dose of UFH 3 times a day to prevent postoperative VTE in cancer patients; pharmacological prophylaxis should be started 2–12 h preoperatively and continued for at least 7–10 days • Chemotherapy: Prophylaxis is not recommended routinely. However, primary pharmacological prophylaxis of VTE is recommended in patients receiving immunomodulators with steroids and/or chemotherapy, and may be indicated in patients with locally advanced or metastatic pancreatic or lung cancer treated with chemotherapy and having a low bleeding risk	LMWH	LMWH >3 months	After 3–6 months, termination or continuation of anticoagulation should be based on individual evaluation of the benefit-risk ratio, tolerability, patient preference, and cancer activity
ISTH (107)	• Low-risk outpatients: Routine prophylaxis is not recommended • High-risk outpatients: LMWH for patients with solid tumours (except brain tumours) and a Khorana Score of ≥ 3 • Advanced pancreatic cancer: LMWH for patients with advanced pancreatic cancer starting or receiving systemic therapy • Chemotherapy: LMWHs or aspirin in patients with myeloma receiving thalidomide-based or lenalidomide-based combination regimens	–	–	In patients with solid tumours and myeloma anticoagulation should continue for a period of 12 weeks after the initiation of a new systemic therapy regimen In patients with myeloma on aspirin monotherapy, aspirin should be used for the duration of thalidomide-based or lenalidomide-based combination regimens
NCCN (103)	• Surgery: LMWH, fondaparinux, UFH, or warfarin • Inpatient: LMWH, fondaparinux, UFH, or warfarin • Low-risk myeloma patients (outpatient): Aspirin • Chemotherapy: LMWH or warfarin in myeloma patients receiving lenalidomide or thalidomide + dexamethasone and chemotherapy	LMWH (preferred)	LMWH (preferred)	Continue for ≥3 months or for as long as there is active cancer or persistent risk factors

[a]Based on the initiative of the Groupe Francophone Thrombose et Cancer with the collaboration of the Academic Medical Center and the University Medical Center Groningen, and the methodological support of the French Institute of Cancer. ACCP = American College of Chest Physicians; ASCO = American Society of Clinical Oncology; BCSH = British Committee for Standards in Haematology; DOAC = Direct oral anticoagulants; EMS = European Myeloma Network; ESMO = European Society of Medical Oncology; ISTH = International Society on Thrombosis and Haemostasis; LMWF = low molecular weight heparin; NCCN = National Comprehensive Cancer Network; UFH = unfractionated heparin; VKA = vitamin K antagonists; VTE = venous thromboembolism.

meta-analysis of these clinical trials reported that LMWH was associated with a reduced risk of recurrent VTE (RR [95% CI]: 0.60 [0.45–0.79]) and no difference in the risk of major bleeding (RR [95% CI]: 1.07 [0.66–1.73]) relative to VKA in cancer patients who experienced an acute VTE episode (116).

Some evidence suggests that the risk of recurrence and bleeding continues with long-term treatment with LWMH in cancer patients with VTE. The DALTECAN (Dalteparin sodium for the long-term management of venous thromboembolism in cancer patients) study followed patients with active cancer and newly diagnosed VTE treated with dalteparin for 12 months (117). All patients received subcutaneous dalteparin initially at 200 IU kg^{-1} day^{-1} with an 18,000 IU maximal daily dose for the first four weeks. During months 2-12, dalteparin was given in accordance with the body weight of the patients (i.e. ≤56 kg: 7500 IU; 57–68 kg: 10000 IU; 69–82 kg: 12500 IU; 83–99 kg: 15000 IU; >99 kg: 18000 IU) (117). In this study, the incidence of major bleeding and recurrent VTE with LMWH was similar between 7–12 months and 2-6 months (117).

Efficacy of DOACs

Although LMWH monotherapy is the recommended treatment for cancer-associated VTE (100–105), VKAs remain a common treatment strategy, especially in some regions of the world (118–120). According to one retrospective study of medical records, the low use of LMWH monotherapy in cancer patients is in part due to the patients' unease with long-term injections (120). Unlike parenteral anticoagulants, direct oral anticoagulants (DOACs), such as direct thrombin inhibitors (i.e. dabigatran) and direct factor Xa inhibitors (i.e. apixaban, rivaroxaban, and edoxaban), offer the convenience of oral administration and have more predictable pharmacodynamics and require less frequent laboratory monitoring than VKAs (121). Large phase 3 studies demonstrated that DOACs have similar efficacy and less major bleeding than LMWH/warfarin for the treatment of acute VTE (122). DOACs therefore theoretically offer a good option for treating cancer-associated VTE. However, the efficacy and safety of DOACs in cancer patients with VTE have not been directly assessed in head-to-head trials with LMWH.

To date, there have only been two small studies directly assessing the safety of DOACs in primary or secondary prevention of cancer-associated VTE. A phase 2 pilot study assessed the safety of apixaban (5 mg, 10 mg, or 20 mg once daily) versus placebo for preventing VTE in 125 patients with metastatic cancer who were receiving chemotherapy (ClinicalTrials.gov: NCT00320255) (123). A second study assessed the safety of dabigatran (dosed according creatinine clearance) versus acenocoumarol in the secondary prevention of VTE in 46 patients with malignant cancer and DVT (124). In both studies, DOACs had a safety and tolerability profile in cancer patients similar to what has been reported in the larger clinical trial population (123, 124). In the apixaban study, apixaban also significantly decreased F1+2 levels for all treatment doses versus placebo (123).

In the pivotal phase 3 clinical trials for DOACs in acute treatment of VTE, only approximately 6% of patients had active cancer; of those patients, approximately 20% to 30% had metastatic cancer and approximately 30% were receiving chemotherapy (125–129). As such, the patient population included in these trials was non-representative of the patient population at risk for cancer-associated VTE. In addition, the criteria for defining cancer status at baseline in these studies varied somewhat from those used in the clinical trials assessing efficacy of LMWH in cancer-associated VTE (116). Nevertheless, in subgroup analyses of the pivotal phase 3 VTE clinical trials for rivaroxaban, edoxaban, and apixaban, these DOACs demonstrated a similar risk of recurrent VTE (rivaroxaban, HR [95% CI]: 0.67 [0.35–1.30]; edoxaban, HR [95% CI]: 0.55 [0.16–1.85]; apixaban, RR [95% CI]: 0.56 [0.13–2.37]) and major or clinically relevant nonmajor bleeding (rivaroxaban, HR [95% CI]: 0.80 [0.54–1.20]; edoxaban, HR [95% CI]: 0.72 [0.40–1.30]; apixaban, RR [95% CI]: 0.57 [0.29–1.12]) compared with LMWH/warfarin (126–128). Similarly, dabigatran demonstrated similar risk of VTE or related death (HR [95% CI]: 0.74 [0.20–2.7]) and major bleeding (HR [95% CI]: 1.23 [0.28–5.5]) compared with warfarin in a subgroup analysis of the pivotal phase 3 VTE trials for dabigatran (129). Overall, in a network meta-analysis of all the pivotal phase 3 VTE trials, the risk of recurrent VTE in cancer patients in the pooled DOAC group was modestly lower than in the pooled VKA group (RR [95% CI]: 0.65 [0.38–1.09]), without significantly increased risk of major bleeding (RR [95% CI]: 0.72 [0.39–1.35]) (116).

It should be noted that drugs that strongly affect the CYP3A4 enzyme and/or P-glycoprotein, including many oncology drugs, may alter the pharmacokinetics of DOACs and could interfere with their metabolism and bioavailability. A comprehensive review of potential drug-drug interactions between chemotherapeutic agents and DOACs in 2014 noted that many antimitotic agents, tyrosine kinase inhibitors (not including erlotinib, gefitinib, and sorafenib), and immune-modulating agents have been shown to interact with CYP3A4 and/or P-glycoproteins (130). However, the common platinum-based agents, antimetabolites, and monoclonal antibodies do not seem to significantly interact with DOACs (130). It is important for clinicians to evaluate the potential for drug-drug interactions when prescribing a DOAC and, if necessary, adjust the dose according to prescribing information.

Planned or ongoing clinical trials

The lack of head-to-head trials assessing the efficacy and safety of DOACs vs LMWH monotherapy for the treatment of VTE in cancer patients necessitates further research. To that end, there are several ongoing or planned trials to compare LMWH to apixaban (ClinicalTrials.gov: NCT02585713), to edoxaban (ClinicalTrials.gov: NCT02073682; Hokusai VTE-cancer) (131), and to rivaroxaban (ClinicalTrials.gov: NCT02583191; CONKO_011/AIO-SUP-0115/Ass and ISRCTN Registry: 86712308; Select-D) (132) in cancer patients with VTE. There is also an ongoing trial to evaluate the efficacy and safety of rivaroxaban vs placebo for reducing the risk of VTE in ambulatory cancer patients receiving

cancer therapy (ClinicalTrials.gov: NCT02555878; CALLISTO). In addition, the Thrombosis Working Party of the Korean Society of Haematology is currently conducting an open-label prospective study of the efficacy and safety of rivaroxaban in Asian patients with cancer-associated VTE (ClinicalTrials.gov: NCT01989845). An open-label study of the efficacy and safety of apixaban in cancer patients with VTE is also planned (ClinicalTrials.gov: NCT02581176; CAPS Study).

Discussion

For more than 150 years, clinicians have recognised that cancer patients are at an increased risk for developing acute VTE events relative to the general population. The incidence of cancer-associated VTE varies by tumour-related factors (most importantly cancer site and stage), patient-related factors, and treatment-related factors (e.g. cancer surgery, chemotherapy, and supportive treatments). All aspects of Virchow's triad may play a role in cancer-associated VTE, including the increased immobility that follows cancer surgery and chemotherapy-induced endothelial damage. Further, accumulating evidence suggests that cancer itself induces directly or indirectly a state of hypercoagulability that is driven in part by the release of procoagulant factors, such as TF, from malignant tissue as well as by inflammation-driven activation of endothelial cells and platelets.

The development of VTE in cancer patients is related to increased morbidity, mortality, and medical costs. The poor prognosis and increased disease burden associated with VTE in cancer necessitates the need for effective therapy and the development of risk stratification models to identify patients most in need of thromboprophylaxis to prevent VTE. To that end, biomarkers, including D-dimer, sP-selectin, and thrombin generation parameters have been identified and have been used to extend the existing risk stratification models that are based on factors including cancer site, blood count parameters, and BMI. However, these models still lack specificity and do not capture the vast majority of cancer patients that are going to develop VTE during the course of their disease. Further improvement in risk assessment is necessary to identify cancer patients at high or low risk of VTE.

Standard management of VTE involves the use of DOACs or VKAs following heparin. However, presently, LMWH monotherapy is considered the standard of care for the treatment of cancer-associated VTE due to the lower efficacy associated with VKA treatment in cancer patients. DOACs offer a potentially promising treatment option for cancer patients with VTE, but, at this time, treatment guidelines do not recommend their use due the lack of head-to-head studies. To address the lack of data, several clinical trials are currently underway assessing the relative efficacy and safety of DOACs compared with LMWH in treating cancer-associated VTE.

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Conflicts of interest

Cihan Ay received honoraria for lectures from Sanofi, Pfizer/BMS, Daiichi-Sankyo, Boehringer Ingelheim, and Bayer. Ingrid Pabinger received honoraria for lectures and advisory board meetings from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer/BMS. Dr. Cohen reports receiving consulting fees from Aspen, Bayer, Boheringer Ingelheim, BMS, Daiichi-Sankyo, GSK, Johnson and Johnson, Leo Pharma, ONO, Pfizer, Portola, Sanofi, Takeda, XO1; advisory board membership with Bayer, BMS, Daiichi-Sankyo, Johnson and Johnson, ONO, Pfizer, Portola, Sanofi, XO1; payments for lectures including speakers bureau services, payments for preparation of reports and payment for development of educational presentations from, Aspen, Bayer, Boheringer Ingelheim, BMS, Daiichi-Sankyo, GSK, Johnson and Johnson, Medscape, Pfizer, and Portola. He is an advisor to the UK Government Health Select Committee, the all-party working group on thrombosis, the Department of Health, and the NHS, on the prevention of VTE. He is also an advisor to Lifeblood: The Thrombosis Charity and is the founder of the European educational charity the Coalition to Prevent VTE.

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