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REVIEW ARTICLE

Cancer and venous thromboembolic disease: from molecular mechanisms to clinical management

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ABSTRACT

Venous thromboembolism (VTE) represents a major challenge in the management of patients with cancer. The malignant phenotype is associated with derangements in the coagulation cascade that can manifest as thrombosis, hemorrhage, or disseminated intravascular coagulation. The risk of VTE is increased by a factor of approximately 6 in patients with cancer compared with non-cancer patients, and cancer patients account for approximately 20% of all newly diagnosed cases of VTE. Postmortem studies have demonstrated rates of VTE in patients with cancer to be as high as 50%. Despite that prevalence, VTE prophylaxis is underused in hospitalized patients with cancer. Studies have demonstrated that hospitalized patients with cancer are less likely than their non-cancer counterparts to receive VTE prophylaxis. Consensus guidelines address the aforementioned issues and emerging concepts in the area, including the use of risk-assessment models, biomarkers to identify patients at highest risk of VTE, and use of anticoagulants as anticancer therapy. Despite those guidelines, a gulf exists between current recommendations and clinical practice; greater efforts are thus required to ensure effective implementation of strategies to reduce the incidence of VTE in patients with cancer.

KEY WORDS

Venous thromboembolism

1. INTRODUCTION

Armand Trousseau first described thrombophlebitis as a presenting sign of visceral malignancy more than 150 years ago. Since then, the effect of cancer on blood coagulation and management has remained a major challenge for multidisciplinary care providers[1]. As a consequence, patients with cancer can experience complications including thrombosis, bleeding, and disseminated intravascular coagulation[2]. Prevention and management of those complications in cancer patients can significantly affect patient treatment, prognosis, and quality of life.

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism, might precede or coincide with a diagnosis of cancer. In this patient group, VTE can potentially complicate surgery, hospitalization, or systemic chemotherapy[3–5]. Risk for VTE is increased by a factor of approximately 6 in patients with cancer compared with non-cancer patients, and patients with cancer account for 20% of all newly diagnosed cases of VTE[6]. Postmortem studies suggest that the incidence of VTE in cancer patients might be as high as 50%, in keeping with the finding that, after cancer itself, VTE represents the second leading cause of death in hospitalized patients with cancer[7–9].

Venous thromboembolism is associated with high morbidity, mortality, and economic burden. Its diagnosis and management can interrupt essential cancer therapy and cause potentially serious bleeding complications[10]. Moreover, approximately 25% of cancer patients with VTE require readmission because of bleeding or recurrent VTE[11,12].

2. MECHANISMS UNDERLYING THE CANCER-ASSOCIATED PROTHROMBOTIC PHENOTYPE

Direct and indirect mechanisms contribute to the pathogenesis of cancer-associated VTE[13–15] (Figure 1). The prothrombotic state variably results from tumour- and patient-specific factors, including vascular compression, vessel injury, use of intravascular devices, administration of systemic chemotherapy, and blood hypercoagulability[16,17]. Cancer-mediated hypercoagulability can result from direct activation of procoagulant pathways by cancer cells or from indirect systemic effects of cancer on a variety of cell types, including leukocytes and endothelial cells[18].

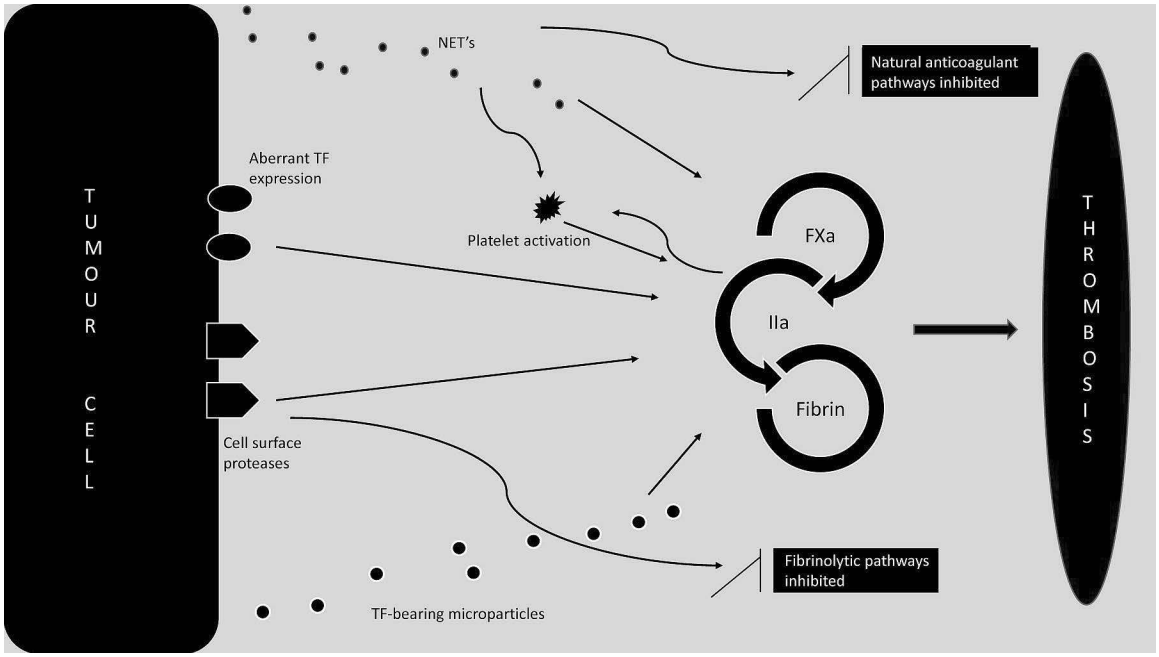

FIGURE 1 *Cancer-mediated hypercoagulability occurs as a consequence of direct activation of procoagulant pathways by cancer cells [mediated by aberrant expression of tissue factor (TF) by tumour cells; release of tumour cell–derived, TF-expressing microparticles; and cancer procoagulant and other cell-surface proteases] or of indirect systemic effects of cancer on a variety of cell types, including leucocytes, endothelial cells, and platelets. In various malignancies, neutrophils are "primed" to release their contents in the form of neutrophil extracellular traps, resulting in direct activation of procoagulant pathways, platelet activation, and inhibition of naturally occurring anticoagulant pathways, including TF pathway inhibitor. As a consequence of these various direct and indirect mechanisms, patients with cancer have an elevated risk of venous thromboembolism.*

2.1 Direct Procoagulant Effects of Cancer Cells

2.1.1 Tissue Factor Expression

Full-length tissue factor (TF) is a 47-kDa transmembrane glycoprotein that binds to coagulation factor VII and activated coagulation factor VII (FVIIa), triggering blood coagulation[19]. Under usual circumstances, TF is not exposed to flowing blood, but rather is expressed on cells in the extravascular compartment. Thus, TF forms a hemostatic "envelope" that attenuates bleeding upon exposure to flowing blood during vascular injury[19].

However, in certain situations (including sepsis[20] and malignancy[21]), aberrant TF expression on a variety of cell types can result in its exposure to the intravascular compartment, with an associated potential for coagulation activation. Mechanisms underlying aberrant cancer-associated TF expression include hypoxia-induced signalling, epidermal-to-mesenchymal transformation, and mutation of tumour suppressor genes including *TP53* (reviewed in van den Berg *et al.*[21]).

Cancer-associated TF expression has several consequences. The membrane-bound full-length TF–FVIIa complex, coupled with cell surface integrins, triggers signalling through an interplay between protease-activated receptor 2 cleavage and TF cytoplasmic domain phosphorylation[22,23]. Those signalling pathways modulate angiogenesis and tumour growth. Emerging evidence suggests that an alternatively-spliced soluble form of TF that lacks a transmembrane region and that has low affinity for FVIIa can also interact directly with cellular integrins and initiate pro-angiogenic signalling (reviewed in van den Berg *et al.*[21]). Secondly, TF–FVIIa directly activates coagulation by cleaving and activating factor X, resulting in prothrombin activation and thrombin generation[19]. Thrombin then activates platelets and feeds back to propagate blood coagulation through activation of factors V and VIII (cofactors for factor X and for prothrombin activation respectively). Finally, cell-surface microparticles derived from tumour cells express TF and are also capable of activating blood coagulation (as described next).

2.1.2 Tumour-Derived TF-Bearing Microparticles

Cancer cells of various types, particularly those of epithelial origin, can spontaneously release small (0.1–1 μm) TF-bearing particles, called "microparticles" (reviewed in Geddings and Mackman[24]). Microparticles promote coagulation because they express not only TF, but also negatively-charged phospholipids, including phosphatidylserine. Tumour-derived microparticles that express TF have been shown to promote thrombosis *in vivo*[24].

2.1.3 Expression of Cell-Surface Proteases

Cancer cells variably express cell-surface enzymes that are capable of direct modulation of procoagulant and fibrinolytic mechanisms. Cancer procoagulant is a cysteine protease expressed on the surface of many cancer cells that directly activates factor X and thus promotes thrombin generation[25]. Cancer cells can also express proteases that modulate fibrinolytic pathways, including tissue plasminogen activator and plasminogen activator inhibitors I and II[26].

2.2 Indirect Procoagulant Effects of Malignancy

2.2.1 Enhanced Formation of Neutrophil Extracellular Traps

Neutrophils are major effectors of innate immunity, engulfing and phagocytosing invading microorganisms. Recently, the role of innate immune cells in inducing thrombosis has been further characterized by the novel identification of neutrophil extracellular traps (NETS). These extracellular fibres are released upon neutrophil degranulation in response to proinflammatory stimuli and are composed of a matrix of granule and nuclear constituents, including DNA and histones[27]. Not only do NETS contribute to direct bacterial killing[27], but they also directly activate procoagulant mechanisms[28]. Constituents of NETS bind to and activate platelets, enhance the activity of neutrophil elastase (which inactivates the anticoagulant molecule TF pathway inhibitor), and contain components that directly activate the contact pathway of blood coagulation[29]. Recently published *in vivo* data indicate that various cancer types are associated with a systemic environment that predisposes peripheral blood neutrophils to NETosis and promotes venous thrombosis[30].

2.2.2 Other Mechanisms Contributing to the Indirect Procoagulant Effect of Malignancy

In addition to the foregoing recently described mechanisms, other factors that likely contribute to the increased VTE risk in cancer patients include altered plasma levels of proinflammatory cytokines and coagulation factors[18,31].

3. RISK FACTORS AND BIOMARKERS FOR CANCER-ASSOCIATED VTE

The risk of VTE in patients with cancer is highest in patients receiving systemic chemotherapy and in those hospitalized on medical and surgical wards. Clinical risk factors for VTE in patients with cancer can be patient-related, cancer-related, and treatment-related (Table I).

Advanced age, obesity, and the presence of comorbidities including infection, anemia, and renal or pulmonary disease modulate individual VTE risk[32]. The VTE risk also varies considerably depending on the primary site and histologic subtype of the cancer. The highest VTE rates have been reported in patients with pancreatic (19.2%), stomach (15.8%), and lung cancer (13.9%)[33]. Patients with hematologic malignancies, particularly lymphoma, are also at increased risk. The risk appears to be highest within 3 months of the initial cancer diagnosis[33–36]. Elevated pre-chemotherapy leukocyte and platelet counts have also been shown to be associated with a higher incidence of VTE[37,38]. Systemic chemotherapy increases the VTE risk by a factor of approximately 2–6[39,40]. That risk is compounded by the use of central catheters[41]. Supportive therapies, including the use of erythropoiesis-stimulating agents and red blood cell and platelet transfusions, further elevate the VTE risk[42,43]. Plasma levels of P-selectin, D-dimer, and TF are currently under investigation as predictive tools for identifying patients at elevated VTE risk[44].

Recently published consensus guidelines from the American Society of Clinical Oncology discourage the use of single risk factors to guide clinical decision-making[45]. A risk assessment model for chemotherapy-associated VTE that assigns scores to 5 predictive variables has recently been developed and validated (Table II)[46]. In addition to identifying patients who are at highest risk of VTE, the risk score has also been shown to predict favourable outcomes

TABLE I Risk factors for venous thromboembolism in patients with cancer

Patient-related	Age, ethnicity, comorbidities (for example, obesity, infection, renal and pulmonary disease)
Cancer-related	Primary site, histologic subtype, natural history of cancer
Treatment-related	Indwelling catheters, systemic chemotherapy, supportive therapies (for example, erythropoiesis-stimulating agents, red blood cell and platelet transfusions)

TABLE II Risk assessment model developed by Khorana *et al.*[46]

Patient characteristic	*Score*
Cancer site	
Very high risk[a]	2
High risk[b]	1
Platelet count ≥ 350,000/mm^3	1
Leukocyte count > 11,000/mm^3	1
Hemoglobin < 10 g/dL or use of ESAS	1
Body mass index ≥ 35	1

[a] Stomach, pancreas.
[b] Lung, lymphoma, gynecologic, and genitourinary (excluding prostate).
ESAS = erythropoiesis-stimulating agents.

from chemotherapy. Currently published guidelines recommend that risk assessment in the outpatient setting should use this model[45].

4. THROMBOPROPHYLAXIS IN CANCER PATIENTS

Despite the well-established prevalence of VTE in cancer patients, the Fundamental Research in Oncology and Thrombosis survey demonstrated that fewer than 5% of patients with cancer hospitalized on medical wards receive thromboprophylaxis[47]. Current consensus guidelines include recommendations for primary thromboprophylaxis in hospitalized cancer patients on medical and surgical wards and in carefully selected ambulatory patients[48].

4.1 Thromboprophylaxis in Hospitalized Medical Patients with Cancer

Three large-scale randomized controlled trials (RCTS) in acutely ill hospitalized medical patients demonstrated reduced rates of VTE in patients receiving prophylactic low molecular weight heparin (LMWH). Those trials explored the clinical efficacy of enoxaparin, dalteparin, and fondaparinux in VTE prevention[49–51]. Although patients with cancer have a significantly higher VTE risk than do hospitalized medical patients without cancer, cancer patients constituted only a minority (5%–15%) of the RCT populations. To date, no published RCT has specifically assessed VTE prophylaxis solely in hospitalized patients with cancer.

Several recently published consensus guidelines promote thromboprophylaxis in all patients admitted to hospital with a diagnosis of cancer in the absence of contraindications[48,52]. Despite the recommendations of those and other guidelines, thromboprophylaxis remains underused in hospitalized patients with cancer[53–55]. In fact, the probability of receiving appropriate thromboprophylaxis has been reported to be lower in patients with cancer than in non-cancer patients[56].

4.2 Thromboprophylaxis in Ambulatory Patients with Cancer

A number of studies have explored the role of primary thromboprophylaxis in ambulatory patients with cancer. Those studies pertain to the period during which cancer patients are not in hospital for surgery or end-of-life care, but are living at home and receiving anticancer therapy as outpatients[57]. In women with metastatic breast cancer receiving chemotherapy, low-dose warfarin was associated with a VTE risk reduction of 85% (compared with placebo)[58]. Subsequently, 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 either nadroparin or placebo, and reported a significant reduction in the composite endpoint of arterial and venous thrombosis[59].

More recently, the SAVE-ONCO trial randomly assigned patients with metastatic or locally advanced solid tumours commencing chemotherapy to receive either the ultralow molecular weight heparin semuloparin or placebo. Despite the relatively low incidence of VTE in the control arm (3.4%), the study demonstrated a significant reduction in the incidence of VTE in patients receiving semuloparin (1.2%), with no apparent increase in the incidence of major bleeding[60]. Similarly, the FRAGEM and CONKO 004 trials explored thromboprophylaxis in patients with locally advanced pancreatic cancer undergoing systemic chemotherapy and demonstrated a combined VTE risk reduction of 12.5%[61,62].

Cumulatively, the randomized trials suggest that thromboprophylaxis with LMWH can be considered in carefully selected outpatients with solid tumours receiving systemic chemotherapy. As discussed earlier, thalidomide and lenalidomide are associated with a very high VTE risk when used in combination with dexamethasone. Consequently, published consensus guidelines recommend that patients with multiple myeloma receiving either regimen should receive thromboprophylaxis with aspirin or LMWH[48].

4.3 Thromboprophylaxis in Surgical Patients with Cancer

Compared with cancer-free patients, those with cancer undergoing surgery are estimated to have a VTE risk that is elevated by a factor of 2–3[6,63–65]. A meta-analysis evaluating clinical trials in which patients were randomly assigned to receive either low-dose unfractionated heparin (UFH) or LMWH revealed similar efficacy and safety in preventing screen-detected VTE[66]. A variety of mechanical thromboprophylactic methods have also been evaluated, but in general, they have been shown to be less effective than pharmacologic prophylaxis[67,68].

The ideal duration of VTE prophylaxis in patients with cancer undergoing major surgery remains unclear. The ENOXACAN II study randomly assigned patients with cancer undergoing laparotomy to receive either short-duration (7–10 days) or extended-duration (28 days) postoperative VTE prophylaxis with enoxaparin (40 mg once daily). At the end of the study period, both groups underwent screening venography. The incidence of DVT was significantly lower in the extended-duration therapy group than in the short-duration therapy group (12% and 4.8% respectively, $p = 0.02$). Follow-up at 3 months demonstrated that the benefit of extended-duration thromboprophylaxis was retained[69].

In another study of patients undergoing laparotomy, a subset of whom underwent the procedure for

malignancy, patients received open-label in-hospital dalteparin for 7 days postoperatively. At discharge, patients were randomly assigned to a group receiving no further VTE prophylaxis and a group receiving dalteparin for a further 20 days. The incidence of DVT was reduced by 55%, to 7.3% in the extended-duration group from 16.3% in the short-duration group ($p = 0.012$)[70].

More recently, the SAVE-ABDO trial compared the efficacy of semuloparin started preoperatively with enoxaparin started postoperatively in patients undergoing major surgery. Although a lower incidence of bleeding was reported in the semuloparin group, no difference was observed with respect to VTE rates or all-cause mortality[48]. Similarly, Simonneau *et al.*[71] randomly assigned patients with colorectal cancer undergoing surgery to receive either nadroparin or enoxaparin preoperatively. Despite a reduction in the rates of major bleeding in the nadroparin group, there was no significant difference in symptomatic or asymptomatic VTE occurrence.

Current consensus guidelines recommend that "all patients with malignant disease undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis with either UFH or LMWH" unless contraindications exist and that VTE prophylaxis should commence preoperatively. Moreover, it is recommended that pharmacologic thromboprophylaxis 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[48].

5. VTE TREATMENT AND SECONDARY PROPHYLAXIS IN CANCER PATIENTS

Based on published evidence from randomized trials[72], currently published consensus guidelines recommend the use of LMWH in preference to UFH for the initial 5–10 days of anticoagulant therapy in patients with cancer and confirmed VTE. After that, LMWH should be continued for 6 months for secondary prophylaxis, and anticoagulant therapy can potentially be extended beyond the initial 6-month period in patients with active malignancy. The insertion of a vena cava filter is recommended only in patients with contraindications to anticoagulant therapy and in whom proximal extension of thrombosis occurs despite maximal LMWH therapy[48,73].

A meta-analysis comparing LMWH and UFH in the treatment of VTE demonstrated a significant reduction in the rates of VTE recurrence and major bleeding in individuals receiving LMWH[74]. A further meta-analysis of RCTs revealed that 3-month mortality was significantly lower in patients receiving LMWH than in those receiving UFH[75]. No significant difference in mortality has been demonstrated between LMWH and vitamin K antagonists (VKAs) in patients with cancer[76]. However, with respect to VTE recurrence, LMWH has been shown to be superior to warfarin as a maintenance therapy in patients with cancer[77]. The CLOT RCT randomly assigned patients with cancer-associated VTE to receive either therapeutic dalteparin or warfarin for 6 months. In patients treated with dalteparin, that study demonstrated an absolute risk reduction of 8% (9% vs. 17%) and a relative risk reduction of 52% ($p = 0.002$; hazard ratio: 0.48) for recurrent VTE[72].

Despite the body of evidence supporting the superiority of LMWH over VKA in the treatment of cancer-associated VTE, long-term treatment with LMWH remains suboptimal with respect to patient preference and cost. Indeed, data from the Swiss Venous Thromboembolism (SWIVTER) and MASTER registries demonstrated that a large proportion of patients with cancer-associated thrombosis still receive warfarin as long-term treatment (51% and 62% respectively)[78,79].

5.1 Use of Novel Oral Anticoagulants

Newer anticoagulants, such as the direct factor IIa and Xa inhibitors, are currently being investigated for use in patients with cancer[80]. Currently published phase III trial data suggest that that novel oral direct inhibitor therapy is at least as safe and efficacious as heparin or VKA therapy in the prevention and treatment of acute VTE in specific clinical scenarios[81–85]. Furthermore, the new agents offer a number of advantages over conventional therapies, including, in general, no requirement for laboratory monitoring, feasibility of oral administration, and reduced drug and food interactions[86].

The EINSTEIN DVT study randomly assigned patients with acute DVT to receive either rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) or conventional therapy with enoxaparin followed by VKA. In that study, rivaroxaban was demonstrated to be noninferior to standard treatment with respect to VTE recurrence (2.1% vs. 3%), and the rate of non-major bleeding was similar in both groups. A subgroup analysis of the trial exploring the safety and efficacy of rivaroxaban in patients with active malignancy demonstrated no significant difference in VTE recurrence or bleeding complications between the two groups[83]. Similarly, the EINSTEIN-PE study reported the noninferiority of rivaroxaban compared with LMWH–VKA treatment in patients with acute symptomatic pulmonary embolism, with no significant difference in major or non-major bleeding complications reported between the groups[84]. The recently published AMPLIFY trial demonstrated the noninferiority of the oral factor Xa inhibitor apixaban compared with conventional therapy in patients with acute VTE. Moreover, major bleeding occurred less frequently in the apixaban group (0.06% vs. 1.8%, $p < 0.001$)[81].

The orally administered direct thrombin inhibitor dabigatran has also been studied in patients with acute symptomatic VTE. The RE-COVER study randomly assigned patients with acute VTE to receive either dabigatran (150 mg twice daily) or warfarin for 6 months. Rates of VTE recurrence were similar in both groups (2.4% in patients receiving dabigatran, 2.1% in patients treated with warfarin), and there was no significant difference in major bleeding. In a subgroup of patients with active cancer, a nonsignificant difference in the risk of VTE recurrence (3.1% in the dabigatran group vs. 5.3% in those treated with warfarin) was observed[85].

Overall, the safety and efficacy of novel oral direct inhibitor therapy in patients with cancer remains unknown. Given the paucity of data supporting the efficacy of these agents and cognizant of potential bleeding complications, published consensus guidelines do not currently recommend their use in patients with malignancy[48].

6. ANTICOAGULANTS AS ANTICANCER THERAPY

A growing body of *in vitro* and *in vivo* evidence suggests that not only do anticoagulant medications prevent and treat VTE in cancer patients, but that they also influence cancer cell biology and patient survival. The mechanisms by which heparins might exert anticancer effects are complex and comprise anticoagulant and non-anticoagulant mechanisms alike (reviewed in Cunningham *et al.*[87] and Casu *et al.*[88]).

The anticoagulant activity of heparin is mediated through a specific interaction with the serine protease inhibitor antithrombin. This heparin–antithrombin interaction results in enhanced inactivation of activated coagulation proteases, particularly factor Xa and thrombin. Recently published data demonstrate that not only do these activated coagulation proteases play a role in blood coagulation, but that they also initiate signalling pathways[89,90]. Downstream effects of coagulation protease–induced signalling might have an impact on cancer biology[91,92]. Moreover, fibrin protects cancer cells from natural killer cell–mediated immune attack[93] and mediates tumour cell adhesion to the vascular wall[94].

Heparin and LMWH promote endothelial TF pathway inhibitor release that might impair TF-mediated proangiogenic and proinflammatory properties (reviewed in Mousa and Petersen[95]). Heparin and LMWH also inhibit the activity of heparanase, an enzyme that is upregulated in cancer and that acts by cleaving cell-surface and extracellular matrix heparan sulphate proteoglycans[87,88,96]. The resultant extracellular matrix disruption facilitates tumour cell invasion. Moreover, degradation of heparan sulphate proteoglycans promotes the release of growth factors implicated in promoting tumour angiogenesis and growth[87,88]. In addition to inhibiting growth factor release, heparin also impairs growth factor–mediated mitogenic signalling activity by directly preventing their interaction with their receptor[87,88,97]. Heparins might directly bind to selectins, cell adhesion molecules whose expression is increased on tumour cells and that are postulated to promote tumour invasion[96,98]. Finally, heparins have been shown to mediate signalling by direct binding to the surface of a variety of cancer cells *in vitro,* attenuating cellular proliferation[99,100].

The precise effect of heparin on patient survival remains incompletely understood. The FAMOUS study randomized patients with advanced malignancy to LMWH or placebo for 12 months. A nonsignificant trend toward increased survival in the group randomized to LMWH was observed. In a subgroup of patients who were alive 17 months after randomization, use of LMWH resulted in significantly improved survival at 2 and 3 years[101]. A subsequent double-blind RCT randomly assigned patients with either metastatic or locally advanced malignancy to a 6-week course of LMWH nadroparin or placebo and demonstrated a significant survival benefit, albeit with an increased risk of major bleeding complications[102]. In a recent meta-analysis of eleven RCTs exploring the use of anticoagulants in patients with cancer, Kuderer *et al.* reported a significant reduction in mortality in patients treated with anticoagulants[103]. In contrast, a 2006 study demonstrated no survival benefit in patients with advanced cancer receiving LMWH[104]. Future prospective trials will potentially shed further light on the magnitude of the heparin-mediated survival benefit in cancer patients.

7. CONCLUSIONS

Despite the fact that risk of VTE is greatly increased in patients with cancer compared with cancer-free patients, prophylactic strategies remain underutilized. Moreover, even when thromboprophylaxis guidelines are rigorously implemented, uncertainty remains about precisely which outpatient groups should be specifically targeted to achieve the optimal benefit–risk ratio. While the molecular mechanisms underlying the pathogenesis of cancer-associated VTE continue to be unravelled, the precise causation for the prothrombotic state and the interplay between its various mechanisms remain poorly understood. Future research initiatives should focus on translating a detailed knowledge of the underlying mechanisms into predictions about the specific groups of ambulatory patients that are at highest VTE risk and that would benefit most from thromboprophylaxis. Finally, a gulf clearly exists between currently published thromboprophylaxis recommendations for hospitalized patients and actual clinical practice. Greater efforts are required to ensure effective implementation of recommended strategies to reduce the incidence of this potentially life-threatening complication in patients with cancer.

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9. CONFLICT OF INTEREST DISCLOSURES

FNA has served on advisory boards for Bayer and Bristol–Myers Squibb. The remaining authors have no financial conflicts of interest to disclose.

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