Prevention of venous thromboembolism in patients with cancer

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Abstract

Venous thromboembolism (VTE) is major cause of both morbidity and mortality in patients with cancer. Venous thromboembolism, which includes both deep vein thrombosis and pulmonary embolism, affects a sizable portion of patients with malignancy and can have potentially life threatening complications. Accurate assessment of risk as well as diagnosis and treatment of this process is paramount to preventing death in this high risk population. Various risk models predictive of venous thromboembolism in patients with cancer have been developed, and knowledge of these rubrics is essential for the treating oncologist. Subgroups of particular interest are inpatients receiving chemotherapy, postoperative patients after surgical debulking, and patients undergoing radiotherapy. Numerous newer drugs have become available for the prevention of venous thromboembolism in patients with cancer who are at high risk of developing the disease. These include the class of drugs called direct oral anticoagulants, (DOACs) which do not require the same monitoring that other modalities have previously required and are taken by mouth, preventing the discomfort associated with subcutaneous strategies. The appropriate risk stratification and intervention to prevent venous thromboembolism are vital to the treatment of patients with cancer.

Introduction

Venous thromboembolism (VTE) is a frequent, morbid, and in many cases preventable occurrence in patients with cancer. Venous thromboembolism is defined as pathological venous clots, further subcategorized into deep vein thrombosis and pulmonary embolism depending on the location of this process. Throughout this review, venous thromboembolism is inclusive of deep vein thrombosis and pulmonary embolism except where otherwise specified.

Venous thromboembolism is a leading cause of death for patients with cancer and poses significant financial and resource use challenges for the healthcare system. Fortunately, multiple treatment options are available to treat venous thromboembolism once identified, and to decrease the likelihood of venous thromboembolism in certain patients based on risk factors. Because anticoagulation is neither innocuous nor costless, questions of whom to treat and with what agents are paramount, and the recommendations continue to evolve. This review is targeted toward oncological healthcare providers, all of whom will regularly encounter patients with venous thromboembolism or at high risk of venous thromboembolism. We will review the available data about venous thromboembolism incidence, morbidity, management, and prevention in oncological patients, and where sufficient data exist, make specific recommendations.

Sources and selection criteria

After identifying key groups within the oncology space, we selected references for this review to reflect landmark articles that have shaped diagnosis and management of venous thromboembolism over the past 15 years. As part of this examination we identified key trials, including mainly randomized control trials, as well as high quality retrospective studies, which support the use of interventions both in the treatment and prevention of venous thromboembolism in the oncological population. The three groups within this cohort included outpatients receiving treatment (chemotherapy or radiation, or both), inpatients (both long term and short term) receiving chemotherapy, and postoperative patients undergoing surgical intervention to treat their cancer. We searched PubMed and Embase and selected peer reviewed articles in the English language that identified data which were used in the prevention of venous thromboembolism in the global oncologic population. The main search items used were venous thromboembolism (VTE), deep venous thrombosis (DVT), pulmonary embolism (PE), and cancer/

Table 1 | Venous thromboembolism risk factors[7 8]

Patient factor	Disease factor	Treatment factor
Body mass index (<18.5 or >30)	Cancer site (mullerian, central nervous system, leukemia/lymphoma, pancreas, renal, gastric)	Systemic therapy
Admission to hospital	cancer stage	Progestin use
Nursing home confinement	Liver metastasis	Central venous catheter
Central venous catheter		Perioperative state
Hereditary hypercoagulability		
Recent or active infection		

oncologic patients. After identification of these studies, they were grouped into the aforementioned cohorts. National Comprehensive Cancer Network guidelines from the United States were also used to validate the conclusions. Randomized controlled trials, meta-analyses, and high impact reviews were used, while non-peer reviewed journals, case reports, and non-English medium journals were excluded.

Epidemiology and risk factors

Trousseau observed as early as 1865 an association between malignancy and venous thrombosis, and over a century of subsequent inquiry has confirmed his initial finding.[1] The annual incidence of venous thromboembolism in the general population is roughly 100 cases per 100 000 people (0.1%), with roughly one third meeting criteria for pulmonary embolism.[2] The incidence of venous thromboembolism and pulmonary embolism in patients with cancer is substantially higher than in the general population. Clinically evident venous thromboembolism has been noted in 2-15% of patients with cancer, and the incidence could be higher if considering subclinical disease.[1 3 4] A multivariate analysis from California identified cancer as the greatest individual risk factor for venous thromboembolism, followed by traumatic injury, recent surgery, and pregnancy.[5] Specific oncological populations at greater risk for venous thromboembolism include patients with metastatic disease, multiple comorbidities, infections, life expectancy <1 year, perioperative patients, and patients actively on treatment. Novel therapeutics, including targeted therapeutics and immune checkpoint inhibitors, remain associated with an elevated risk of venous thromboembolism; as do additional chemotherapeutics (any systemic therapy appears to be a risk factor for venous thromboembolism).[6] Pancreatic, renal, gastric, ovarian, lung, and esophageal cancers as well as glioblastoma are primary sites of cancer that confer a substantial risk of venous thromboembolism (table 1).[5 9 10]

Among patients with unprovoked (idiopathic) venous thromboembolism, one study showed a 5.2% likelihood of occult malignancy, and multiple cohort studies have showed a three to four times increased likelihood of occult malignancy over matched controls.[1 11-14] Cancer patients are also more likely to have recurrent venous thromboembolism, including when they are on appropriate anticoagulants.[3 7] The incidence of venous thromboembolism is increasing in patients with cancer, possibly owing to increasing comorbidity, but also novel systemic therapies including targeted therapies and immunotherapy that are associated with increased thrombotic risk.[6 15]

Not only are patients with cancer at greater risk for venous thromboembolism, but venous thromboembolism is a risk factor for poor outcomes among patients with cancer. Thromboembolism, including venous thromboembolism and arterial events, is the second leading cause of death among patients with cancer, behind only progressive cancer, and has a similar incidence to infection.[6 16] In-hospital mortality for patients with cancer and venous thromboembolism is over twice that of mortality for matched patients without venous thromboembolism.[9] Pulmonary embolism can cause mortality directly, but venous thromboembolism is also associated with higher all cause mortality in patients with cancer, plausibly because coagulopathy is a manifestation of unfavorable tumor biology or other suboptimal patient factors.[15 17]

Pathogenesis

The pathophysiology of venous thromboembolism explains the increased incidence in patients with cancer and offers insights into some of the therapeutic interventions aimed at preventing and treating venous thromboembolism. Three factors classically associated with venous thromboembolism are: disruptions in venous blood flow (namely, stasis, turbulence, or increased viscosity); endothelial or vessel wall injury; and hypercoagulability; these factors are commonly referred to as Virchow's triad (fig 1).[1] That cancer can contribute to all of the above mechanisms of pathogenic clot formation is well known.[1] Immobility, decreased functional status, inpatient admissions, and perioperative status have all been implicated in venous stasis. Von Willebrand factor (vWF), a marker commonly used to assess endothelial damage, has been shown to be elevated in both solid and hematological malignancies, although the mechanisms through which cancer damages endothelium remain under investigation (fig 2). Finally, myriad studies have shown disruptions in both procoagulant and anticoagulant factors in patients with cancer. Excess procoagulant factors including tissue factor, fibrinogen, plasminogen activator inhibitor, and cancer procoagulant have all been shown in patients with cancer, alongside decreased anticoagulant and fibrinolytic factors including antithrombin, proteins C and S, and tissue plasminogen activator. Finally, platelets are often more abundant and more active in patients with

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metastatic cancers.[1] Further work is needed to fully characterize perturbations in coagulation pathways for patients with cancer, and to understand the multifactorial nature of thrombogenesis.

Economic implications

The economic implications of venous thromboembolism and its prevention are worth considering. Patients with cancer and venous thromboembolism tend to have longer hospital admissions, more frequent admissions, and increased healthcare costs.[17 19] Reasonable estimates for the incremental cost of venous thromboembolism are around $10 000 for admission to hospital for a venous thromboembolism, or around $17 000 for a pulmonary embolism in adjusted 2019 US dollars.[19 20] Conditional upon having a venous thromboembolism, recent cost effectiveness analyses have suggested that direct oral anticoagulants (DOACs) are equally or less expensive than low molecular weight heparin (LMWH) in patients with cancer.[21] Also worth considering are the costs of pharmacological prevention of venous thromboembolism. Factors influencing cost effectiveness of thromboprophylaxis include the cost of the agent, cost per admission to hospital for venous thromboembolism, and cost per admission for sequelae of bleeding. Initial cost effectiveness analysis looking at DOACs in patients with cancer with intermediate to high risk of venous thromboembolism suggest DOACs are cost effective in this scenario, and that a Khorana score ≥3 is the most cost effective risk stratification tool.[19]

Venous thromboembolism in patients with cancer receiving systemic therapy

Recent studies have shown a substantial increase in risk of venous thromboembolism in people with cancer. For instance, in a Danish cohort study, people with a cancer diagnosis in 1997 had a 12 month venous thromboembolism incidence of 1%, increasing to 1.9% in 2004 and to 3.4% in 2017.[22] In contrast, no substantial increase in risk of venous thromboembolism in people without cancer was observed in the same period. Many have postulated that some of this risk could be related to increased use of systemic therapy. Chemotherapy has always been associated with an increased risk of venous thromboembolism; more recent studies have also suggested that newer anticancer agents, including targeted therapy and immunotherapy, might also be associated with increased risk of venous thromboembolism. In the same cohort study, chemotherapy (standardized hazard ratio 3.4; 95% confidence interval 3.1 to 3.7), protein kinase inhibitors (standardized hazard ratio 4.1; 3.4 to 4.9), anti-angiogenic therapy (standardized hazard ratio 4.4; 3.8 to 5.2), and immunotherapy (standardized hazard ratio 3.6; 2.8 to 4.6) were all risk factors for venous thromboembolism in multivariable analysis.[22] Several other recent cohort studies have also shown a high prevalence or incidence of venous thromboembolism in patients with cancer receiving immunotherapy, particularly immune checkpoint inhibitors.[23] Caution must be exercised when attributing causality: many of these newer agents, particularly immune checkpoint inhibitors, have substantially increased survival in people with cancer, and therefore the high incidence of venous thromboembolism in people receiving these drugs could be a function of exposure time (time on the treatment). These agents are, however, undoubtedly associated with a higher incidence of venous thromboembolism, and also that venous thromboembolism in patients on either chemotherapy or newer agents is associated with substantially worse survival.[24 25]

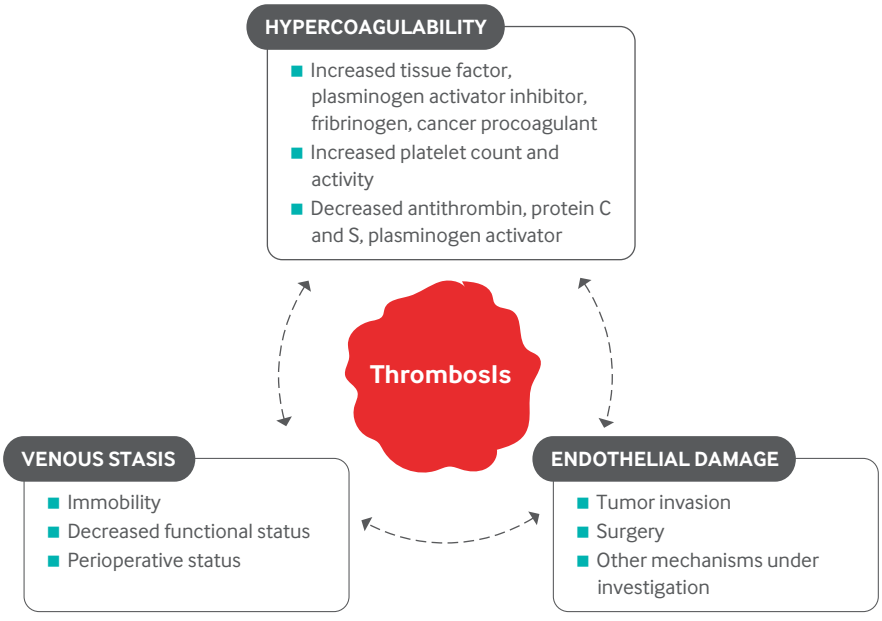

Fig 1 | Virchow's triad

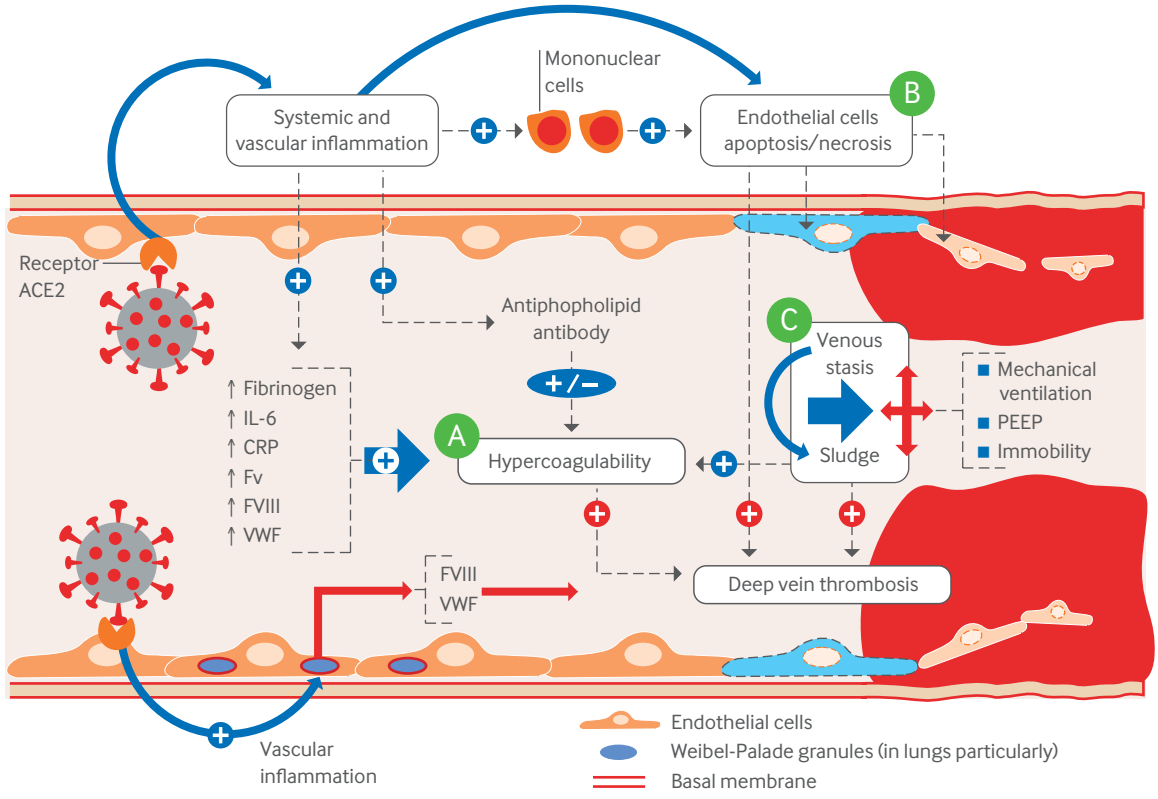

Fig 2 | Pathogenesis of venous thromboembolism[18]

Defining a high risk medical oncology population

Although the increased risk of venous thromboembolism in people with cancer is repeatedly emphasized, it should also be noted that risk is not evenly spread across all patients with cancer. In fact, the risk of venous thromboembolism varies substantially across race (highest in black people[26]; lowest in Asians), type of cancer, healthcare setting (inpatient *v* ambulatory), status of cancer (metastatic *v* remission *v* history of cancer), and as has already been shown, type of treatment. The best known driver of risk is type of cancer. The highest rates of venous thromboembolism have typically been observed in patients with gastric and pancreatic cancers as well as primary brain tumors[27]; lower risk has been seen in people with breast and prostate cancers.[22 27 28] People with hematological malignancies, particularly lymphomas and myeloma, who are receiving specific regimens, are also at elevated risk.

Since the risk of venous thromboembolism in the medical oncology population is multifactorial, risk assessment for venous thromboembolism is best done by using risk assessment tools. The first of these, referred to as the Khorana score, has been widely developed and validated for use in a population of patients with mixed solid tumors (including gynecological cancers and lymphomas)[29]; a recent study has also validated use of the Khorana score with modifications in an Asian population. The Khorana score uses a combination of type of cancer, components of the complete blood count (including low hemoglobin and elevated platelet or leukocyte counts), and body mass index to determine risk (table 2). In the original study, high risk was defined as a score of 3 or higher, while some subsequent validation studies and meta-analyses use a score of 2 or higher to identify a larger population of at-risk patients.[30] Two recent randomized trials of thromboprophylaxis used a score of 2 as a cut-off to determine consideration for prophylaxis.[31 32] A more recent validated score keeps the original categorization by cancer type from the Khorana score but uses varying levels of D-dimer to assign risk.[33] Importantly, some attempts to validate the Khorana score and similar scoring systems suggest that they fail to identify a substantial portion, if not a majority, of oncological patients with venous thromboembolism.[34] Ongoing studies are evaluating ways to improve risk prediction and are particularly focused on biomarker development and validation. Multiple myeloma also confers a high risk of venous thromboembolism, and additional models, included the SAVED and IMPEDE scoring systems, have been validated to predict the risk of clots in this population.[35]

Recommendations for oncology and chemotherapy patients admitted to hospital

The American Society of Clinical Oncology,[36] American Society of Hematology,[37] International Initiative on Thrombosis and Cancer,[38] and the National Comprehensive Cancer Network[39] publish comprehensive, evidence based, and regularly updated guidelines on primary prevention of

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Table 2 | Khorana score for estimating venous thromboembolism risk in patients with cancer

Metric	Points
Very high risk cancer: pancreas, stomach	2
High risk cancer: gynecological, testicular, bladder, lymphoma, lung	1
All other cancers	0
Thrombocytosis ≥350K/µL	1
Pre-chemotherapy white blood cell count >11K/µL	1
Body mass index ≥35kg/m2	1
Hemoglobin <10 g/dL	1
Use of erythropoietin stimulating agent	1
Khorana score	Intervention
0-1 (Low risk)	No prophylaxis indicated
2 (intermediate risk)	Consider prophylaxis
≥3 (high)	Prophylaxis indicated

venous thromboembolism in the setting of malignancy. While these guidelines highlight many consistent themes (most notably the high risk of venous thromboembolism for patients with advanced and recurrent cancer, the importance of risk stratification, and the critical need to identify evidence based approaches to primary prevention), the committees reach different conclusions, both with regard to the strength of the recommendations and the recommendations themselves. The guidelines consider each unique clinical setting and the variety of regimens commercially available including, aspirin, unfractionated heparin, vitamin K antagonists, LMWH, fondaparinux, and DOACs. While some recommendations cross disease sites, others specify high risk sites such as pancreas, multiple myeloma, and lung.

When considering implementation of the consensus recommendations for an individual patient, emphasis is uniformly placed on considering a wide range of factors including efficacy of the regimen in decreasing the risk of clinically relevant outcomes (all venous thromboembolism, symptomatic venous thromboembolism, pulmonary embolism, or mortality), risk of bleeding (active, major, or clinically significant), medical comorbidities (renal function, platelet count, obesity, etc), financial costs, risk of clot (mortality, treatment delays, etc), and patient specific factors (fear of needles, religious prohibitions on use of pork derived drug treatments, distress related to risk of bleeding *v* that of clotting, etc).

Oncology patients admitted to hospital

Although all guidelines recommend venous thromboembolism thromboprophylaxis for patients with cancer admitted to hospital who are at low risk of bleeding, definitive data specific to this patient population to support recommendations for or against the use of venous thromboembolism thromboprophylaxis are surprisingly limited and contradictory in their results.[40] The best available data come from three randomized trials in acutely ill patients admitted to hospital,[41-43] and a meta-analysis of these trials focusing on the subset of 307 patients with cancer. In the meta-analysis, venous thromboembolism thromboprophylaxis did not affect the relative risk of venous thromboembolism compared with placebo in an undefined group of patients with cancer (risk ratio 0.91, 95% confidence interval 0.21 to 4.0), likely owing to the small sample size.[44] In an analysis of patients with cancer used to develop the American Society of Hematology guidelines, venous thromboembolism thromboprophylaxis had no effect on symptomatic proximal deep vein thrombosis, symptomatic distal deep vein thrombosis, or mortality, but did decrease the risk of pulmonary embolism (risk ratio 0.59, 95% confidence interval 0.45 to 0.78).[45] This analysis does emphasize that the rarity of the event, even in a more carefully defined population, will continue to limit the statistical significance of any intervention. Additionally, the fact that up to 45% of venous thromboembolisms occur after discharge and many venous thromboembolisms remain asymptomatic prevents accurate assessment of the extent to which thromboprophylaxis prevents venous thromboembolism.[46] Thus, we are left to extrapolate from randomized trials in acutely ill patients such as PREVENT, ARTEMIS, MEDENOX,[41 47] and associated meta-analyses,[48] which uniformly show benefit from venous thromboembolism thromboprophylaxis.

Recommendations from professional organizations regarding anticoagulation in the inpatient and outpatient settings are detailed in table 3.

Outpatients receiving chemotherapy

Historically, LMWH was the primary option for venous thromboembolism thromboprophylaxis in the ambulatory setting. Recommendations shied away from the use of LMWH, predominantly owing to the risk of bleeding and the variable impact on clinically relevant outcomes such as symptomatic venous thromboembolism and mortality, but also because of cost and patient discomfort.[49 50] In a meta-analysis of 3655 patients unselected by risk assessment, with a history of cancer or active cancer, extended prophylaxis did not decrease venous thromboembolism (odds ratio 0.85, 95% confidence interval 0.61 to 1.18) but did increase risk of clinically relevant bleeding (odds ratio 2.11, 95% confidence interval 1.33 to 3.35).[51] In a 2020 comprehensive Cochrane review, LMWH decreased the risk of symptomatic venous thromboembolism (risk ratio

Table 3 | Current anticoagulation recommendations for inpatient versus outpatient patients with cancer

Guideline	ASCO 2019	ASH	ITAC	NCCN 2002
*Clinical scenario**				
Inpatient				
Medical admissions with an active cancer		Suggests chemoprophylaxis with LMWH over unfractionated heparin and no mechanical prophylaxis		Recommend chemoprophylaxis with dalteparin, enoxaparin, fondaparinux, or unfractionated heparin
Risk stratified	Chemoprophylaxis should be offered to those with active malignancy and acute medical illness or reduced ambulation		Recommend chemoprophylaxis with LMWH, fondaparinux, or unfractionated heparin to those with cancer and reduced mobility	
	Chemoprophylaxis may be offered to those with active malignancy and no other risk factor			
	Chemoprophylaxis should not be offered to those with active malignancy admitted for minor procedure or chemotherapy			
Ambulatory				
All patients with cancer receiving/initiating chemotherapy	Should not be offered chemoprophylaxis			No routine chemoprophylaxis
intermediate-high		Suggests chemoprophylaxis with a DOAC or no chemoprophylaxis		
High risk (eg, Khorana score ≥2)†	May be offered chemoprophylaxis with apixiban, rivaroxaban, or LMWH	Suggests chemoprophylaxis with LMWH or a DOAC	Recommend chemoprophylaxis with a DOAC	Consider chemoprophylaxis with apixiban, rivaroxaban, dalteparin, or enoxaparin for up to 6 mon hs or longer
Multiple myeloma‡	Should be offered chemoprophylaxis with acetylsalicylic acid or LMWH based on risk stratification	Suggests using acetylsalicylic acid, vitamin K antagonist or LMWH	Recommend chemoprophylaxis with acetylsalicylic acid, LMWH, DOAC, or vitamin K antagonist	Recommend chemoprophylaxis (acetylsalicylic acid, LMWH, DOAC, or warfarin based on IMPEDE or SAVED score)
Locally advanced or metastatic pancreatic cancer			Recommend chemoprophylaxis with LMWH or DOACs	
Locally advanced or metastatic lung cancer			Do not recommend chemoprophylaxis with LMWH	

ASCO= American Society of Clinical Oncology; ASH= American Society of Hematology; DOAC=direct oral anticoagulant; ITAC=International Initiative on Thrombosis and Cancer; LMWH=low molecular weight heparin; NCCN= National Comprehensive Cancer Network.
*All scenarios presume active cancer and no contraindication to chemoprophylaxis.
†The ASCO and NCCN guidelines use the Khorana score as the method of risk assessment. The ASH and ITAC guidelines recommend use of a validated score such as the Khorana score.
‡Specific to those patients with multiple myeloma receiving thalidomide based or lenalidomide based regimens with chemotherapy and dexamethasone, or both.

0.62, 95% confidence interval 0.46 to 0.83) in outpatients receiving chemotherapy for a malignancy while also increasing the risk of major bleeding (risk ratio 1.63, 95% confidence interval 1.12 to 2.35) and having no impact on overall mortality after one year (risk ratio 0.94, 95% confidence interval 0.83 to 1.07).[52] In a meta-analysis of 11 953 patients across 22 studies, thromboprophylaxis decreased the incidence of venous thromboembolism (odds ratio 0.51, 95% confidence interval 0.43 to 0.61) with no increase in major bleeding.[53] Similarly, the American Society of Hematology guideline team looked at 12 randomized control trials which used either unfractionated heparin or LMWH, and showed no impact on mortality or major bleeding, but a decrease in all venous thromboembolism (risk ratio 0.57, 95% confidence interval 0.46 to 0.71).

More recently, two randomized trials called AVERT[32] and CASSINI[31] examined the impact of venous thromboembolism thromboprophylaxis with a DOAC on the 180 day incidence of venous thromboembolism in the ambulatory setting. In AVERT, 574 patients were randomized to apixaban versus placebo, and in CASSINI, 841 patients were randomized to rivaroxaban versus placebo. Both studies limited inclusion to those with a Khorana score ≥2. Despite a similar risk profile based on the Khorana score, outcomes in these trials differed, likely owing to cohort characteristics. In CASSINI, routine lower extremity ultrasounds excluded 4.5% of patients before randomization, and increased diagnosis of asymptomatic venous thromboembolism. Additionally, CASSINI had a high risk disease site distribution, with 50% of patients diagnosed with a pancreatic or gastric primary.[54] In AVERT, apixaban decreased the risk of venous thromboembolism to 4.2% from 10.2% in the placebo group (hazard ratio 0.41, 95% confidence interval 0.26 to 0.95). In contrast, the CASSINI trial indicated no difference in the risk of venous thromboembolism when comparing rivaroxaban (6%) with placebo (8.8%) (hazard ratio 0.66, 95% confidence interval 0.40 to 1.09). Bleeding events were higher on anticoagulation in both trials, but only reached statistical significance in the AVERT trial (hazard ratio 2.00, 95% confidence interval 1.01 to 3.95) The American Society of Hematology analysis of these two studies, combined with a phase

2 study,[55] found probable differences in mortality, pulmonary embolism, deep vein thrombosis, and major bleeding, although only pulmonary embolism (risk ratio 0.48, 95% confidence interval 0.24 to 0.98) achieved statistical significance. These findings are consistent with other available meta-analyses.[52 56 57]

Owing to the variability of venous thromboembolism and bleeding events observed across patient populations in these studies, guideline recommendations differ somewhat. Notably, however, each guideline has recommended a risk stratification approach based on a validated score (eg, Khorana score) or the primary disease site (eg, pancreas,[58 59] multiple myeloma,[60 61] or lung[62]).

Patients undergoing radiation

None of the guidelines mention venous thromboembolism thromboprophylaxis for patients undergoing radiation, and fewer data are available to guide clinical practice. Venous thromboembolism during radiation appears to be a less common event, affecting 2% of patients during radiation treatment or in the six months after.[63] Limitations in the data likely stem from the fact that early risk assessment models did not associate radiation with an increased risk of venous thromboembolism,[64-66] and so, further study has been modest. In a more recent subanalysis of the COMPASS-CAT study, radiation was associated with an increased risk of venous thromboembolism (hazard ratio 2.47, 95% confidence interval 1.47 to 4.12), a risk that was more pronounced in women than in men (10.8% *v* 2.7%, p=0.03).[67] In a large registry of patients with newly diagnosed symptomatic venous thromboembolism, 13% of the 9284 patients with active cancer were receiving radiation at the time of the diagnosis.[68] Those receiving radiation were at increased risk of pulmonary embolism, but had the same risk of deep vein thrombosis. Major bleeding episodes were equivalent between those receiving and not receiving radiation, but those receiving radiation had an increased proportion of cerebral bleeds. Chemoradiation was not associated with an increased risk of venous thromboembolism compared with radiation alone. Further investigation is needed to inform recommendations in patients receiving radiation, particularly given concerns regarding cerebral bleeding complications related to anticoagulation during radiation treatment.

Choice of agents for thromboprophylaxis

No randomized trials have compared DOACs with LMWH for primary prevention of venous thromboembolism in patients with cancer undergoing chemotherapy. In a meta-analysis of six randomized studies comparing venous thromboembolism thromboprophylaxis to placebo,[22 32 49 50 69 70] including 7185 patients with active malignancy, venous thromboembolism thromboprophylaxis decreased the risk of venous thromboembolism (risk ratio 0.57, 95% confidence interval 0.41 to 0.78). DOACs and LMWH showed comparable effect on the occurrence of venous thromboembolism (DOAC risk ratio 0.55, 95% confidence interval 0.34 to 0.90; LMWH risk ratio 0.59, 0.37 to 0.95) and major bleeding (DOAC risk ratio 1.95, 0.88 to 4.3; LMWH risk ratio 1.38, 0.88 to 2.14).[71] Support for the use of DOACs in clinical guidelines is based on the previously presented placebo controlled trials and meta-analyses validating their use, as well as better adherence improvements seen with an oral regimen over subcutaneous injections.

While DOACs are commercially available with a Food and Drug Administration indication for venous thromboembolism thromboprophylaxis in acutely ill patients, their use in the inpatient setting is largely limited to patients who were using them before admission. Two large randomized trials have compared DOACs to enoxaparin for prevention of venous thromboembolism in patients admitted to hospital, that include information on the number of patients with cancer. These trials are MAGELLAN[72] with 7% active patients with cancer and ADOPT[73] with 3.2% active patients with cancer. A meta-analysis of these two trials and a third, APEX,[74] which does not report on the number of patients with cancer, concluded that DOACs did not decrease the risk of pulmonary embolism (risk ratio 0.67, 95% confidence interval 0.41 to 1.09), symptomatic deep vein thrombosis (risk ratio 0.62, 0.36 to 1.05), or mortality (risk ratio 1.01, 0.89 to 1.14) when compared with LMWH, but did increase the risk of major bleeding (risk ratio 1.99, 95% confidence interval 1.08 to 3.65).[75] Despite the lack of cancer specific data, LMWH or unfractionated heparin remain the anticoagulants of choice for venous thromboembolism thromboprophylaxis in patients with cancer admitted to hospital.

Surgical oncology patients

The use of prophylactic anticoagulation in surgical oncology patients has been an area of increasing clinical interest, because venous thromboembolism is the second leading cause of death for patients with medically and surgically treated cancer.[76] Both perioperative and extended prophylaxis have been extensively investigated. Regarding perioperative prophylaxis, the prospective, observational, RISTOS project identified venous thromboembolism as the most common cause of death at 30 days in over 2300 patients undergoing oncological surgical interventions for general, urological, or gynecological malignancies.[77]

The clinical practice guidelines of both the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend that all patients with malignant disease who are planning to undergo surgical intervention be offered pharmacological thromboprophylaxis with either unfractionated heparin or LMWH (unless bleeding contraindications are present).[36]

The Cochrane Collaboration examined randomized controlled trials that enrolled individuals with cancer undergoing a surgical intervention and assessed the effect of LMWH or unfractionated heparin or

Table 4 | Current anticoagulation recommendations for postoperative patients with cancer

Society	Recommendation
National Comprehensive Cancer Network	• Consider preoperative dosing with unfractionated heparin or LMWH for high risk surgery (eg, abdominal/pelvic patients) ± intermittent pneumatic compression device • Out-of-hospital primary venous thromboembolism prophylaxis is recommended for up to four weeks postoperatively for high risk abdominal or pelvic cancer surgery patients • Consideration of a DOAC (apixaban) for patients undergoing surgery for gynecological malignancy
American Society of Clinical Oncology	• All patients with malignant disease undergoing major surgical intervention should be offered pharmacological thromboprophylaxis with either unfractionated heparin or LMWH, unless contraindicated because of active bleeding, high bleeding risk, or other contraindications • Prophylaxis should be commenced preoperatively • Mechanical methods can be added to pharmacological thromboprophylaxis but should not be used as monotherapy for venous thromboembolism prevention, unless pharmacological methods are contraindicated because of active bleeding or high bleeding risk • A combined regimen of pharmacological and mechanical prophylaxis may improve efficacy, especially in the highest risk patients • Pharmacological thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7-10 days. Extended prophylaxis with LMWH for up to four weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high risk features, such as restricted mobility, obesity, history of venous thromboembolism, or with additional risk factors. In lower risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis
American College of Chest Physicians	• For patients at high risk of venous thromboembolism undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, extended duration pharmacological prophylaxis (four weeks) with LMWH over limited duration prophylaxis is recommended
European Society of Medical Oncology	• In patients with cancer undergoing major cancer surgery, prophylaxis with LMWHs or unfractionated heparin is recommended. Mechanical methods such as pneumatic calf compression can be added to pharmacological prophylaxis, but should not be used as monotherapy unless pharmacological prophylaxis is contraindicated because of active bleeding • Patients with cancer undergoing elective major abdominal or pelvic surgery should receive in-hospital and post discharge prophylaxis with subcutaneous LMWH for up to one month after surgery

DOAC= direct oral anticoagulant; LMWH=low molecular weight heparin.

fondaparinux on deep vein thrombosis, pulmonary embolism, mortality, bleeding outcomes, and thrombocytopenia.[78] A total of 20 trials and over 9770 patients were included in the analysis. The Cochrane Collaboration found no significant differences between perioperative thromboprophylaxis with LMWH versus unfractionated heparin, nor between LMWH versus fondaparinux, in effects on major bleeding, minor bleeding, mortality, or thromboembolic outcomes in patients with cancer. It did find a reduced incidence of wound hematoma with use of LMWH compared with unfractionated heparin.

Extended prophylaxis refers to postoperative anticoagulation that is continued in the weeks after a cancer related surgery. The 9th edition of the American College of Chest Physicians evidence based clinical practice guidelines recommends that after abdominal or pelvic surgery to treat cancer, four weeks of pharmacological prophylaxis be administered in patients who are defined as high risk for venous thromboembolism, but do not harbor significant risk of bleeding.[79] Interestingly, the guidelines make no reference to a venous thromboembolism risk or bleeding scoring system to inform such risk stratification.

The landmark ENOXACAN I trial established a 15% deep vein thrombosis rate in patients with cancer undergoing abdominal surgery and 10 days of enoxaparin prophylaxis.[80] This trial was followed by ENOXACAN II, which looked to examine the utility of extended length prophylaxis in patients with cancer based on the data from six randomized double blind placebo controlled trials in the orthopedic surgery arena. Earlier data had also suggested that postoperative activation of the coagulation cascade persisted beyond the first 10 postoperative days, with venous thromboembolism incidence remaining elevated; as high as 25% 4-6 weeks after a surgical intervention.[81] ENOXACAN II was designed as a double blind multicenter trial in which patients undergoing planned curative open surgery for abdominal or pelvic cancer received enoxaparin (40 mg subcutaneously) daily for 6-10 days and were then randomly assigned to receive either enoxaparin or placebo for an additional 21 days.[82] Outcome assessment was determined via bilateral venography between days 25 and 31 of study, or sooner in the context of symptoms. The rate of venous thromboembolism at the end of the double blind phase was 12.0% in the placebo group and 4.8% in the enoxaparin group (p=0.02), and this difference persisted after three months of follow-up (13.8% *v* 5.5%, p=0.01). The study authors noted no significant differences in complications, including bleeding.

The utility of pharmacological anticoagulation in combination with mechanical prophylaxis was examined in the Protector randomized clinical trial,[83] specific to patients with gastric carcinoma. Importantly, earlier studies had suggested that the incidence of venous thromboembolism was significantly lower in Asian patients than in US or European trials, suggesting that the risks associated with pharmacological anticoagulation might exceed any potential benefits. A total of 682 patients were enrolled in the trial, with 666 evaluable, all of whom underwent surgical management of gastric adenocarcinoma. All patients received duplex ultrasonography on postoperative day 4. The incidence of venous thromboembolism was significantly higher in the intermittent pneumatic compression alone group (3.6%, 95% confidence interval 2.05% to 6.14%) compared with the intermittent pneumatic compression plus LMWH group (0.6%, 95% confidence interval 0.17% to

2.18%; p=0.008). None of the patients with deep vein thrombosis had any signs or symptoms while on trial, suggesting that the outcome measure might not accurately reflect a meaningful clinical endpoint. An alternate trial of 117 patients undergoing esophagectomy in the context of esophageal cancer showed a significant reduction in deep vein thrombosis when nadroparin calcium was administered twice daily versus once daily (0% *v* 7.27%, p=0.046). Furthermore, the cumulative volume of chest drainage, which was used as a surrogate for bleeding complications associated with anticoagulation, was similar between the two groups (p=0.406). Once again, venous thromboembolism was identified via the use of daily vascular ultrasound of the lower extremities for the first seven postoperative days.[84]

In colorectal cancer, the utility of extended anticoagulation in the postoperative period was examined in a prospective, randomized trial enrolling 301 consecutive patients who underwent minimally invasive surgical approaches.[85] Patients received either short course (one week) or extended (four weeks) pharmacological prophylaxis with heparin. Complete compression ultrasonography of the lower extremities was performed after 8 ± 2 days of antithrombotic prophylaxis. Patients with no evidence of venous thromboembolism were randomized and included in the trial. Complete compression ultrasonography was repeated at day 28 ± 2 after surgery by investigators blinded to treatment allocation. The primary outcome of the study was the composite of symptomatic and ultrasonography. A total of 225 were randomized, and venous thromboembolism occurred in 11 of 113 patients (9.7%) randomized to short heparin prophylaxis, and in none of the 112 patients randomized to extended heparin prophylaxis (p=0.001). The incidence of venous thromboembolism at three months was 9.7% and 0.9% in patients randomized to short or to extended heparin prophylaxis, respectively (relative risk reduction 91%, 95% confidence interval 30% to 99%; p=0.005). The rate of bleeding was similar in the two treatment groups.

In addition to the above studies, two large systematic reviews and meta-analyses support the incorporation of extended prophylactic anticoagulation in the postoperative window for patients with cancer. In a meta-analysis that included 4807 patients from seven randomized and prospective observational cohort trials, extended thromboprophylaxis, defined as 2-6 weeks, was associated with a significantly reduced incidence of all venous thromboembolisms (2.6% *v* 5.6%, risk ratio 0.44, 95% confidence interval 0.28 to 0.70, number needed to treat 39) and proximal deep vein thrombosis (1.4% *v* 2.8%, risk ratio 0.46, 95% confidence interval 0.23 to 0.91, number needed to treat 71).[86] This study found no significant difference in the incidence of symptomatic pulmonary embolism (0.8% *v* 1.3%, risk ratio 0.56, 95% confidence interval 0.23 to 1.40), major bleeding (1.8% *v* 1.0%, risk ratio 1.19, 95% confidence interval 0.47 to 2.97), or all cause mortality (4.2% *v* 3.6%, risk ratio 0.79, 95% confidence interval 0.47 to 1.33). Furthermore, when analyzing randomized trials independently, no outcomes measures differed. Importantly, the deep vein thrombosis endpoints of the three randomized trials included were primarily driven by asymptomatic events detected by on-study mandatory imaging assessments. Only six of 41 patients (14.6%) were symptomatic as the time of diagnosis. As anticipated, the incidence of deep vein thrombosis in the included observational trials was substantially lower than the randomized controlled trial (2.5% *v* 9.3%), because these were definitionally symptomatic patients.

Although adoption of postsurgical venous thromboembolism pharmacological prophylaxis in the population with cancer is well supported by existing data, concerns have emerged related to compliance with daily subcutaneous injections as well as costs. A pivotal clinical trial established oral apixaban as an effective and safe alternative to subcutaneous dalteparin in the treatment of cancer associated venous thromboembolism. No increase in major bleeding was identified.[87] As an extension of that trial, investigators looked to explore the efficacy and safety of apixaban versus enoxaparin for extended postoperative prophylaxis in a gynecological cancer patient population. A two site randomized clinical trial included 400 women undergoing surgery for a known or suspected gynecological malignancy. Enrolled patients were randomized to apixaban 2.5 mg orally twice a day or enoxaparin 40 mg subcutaneously daily for 28 days. Both major bleeding events (0.5% *v* 0.5%; p>0.99) and clinically relevant non-major bleeding events (5.4% *v* 9.7%; p=0.11) were not different between the groups. Venous thromboembolism was assessed for drug efficacy and showed no difference between the groups, with 1.0% in the apixaban group and 1.5% in the enoxaparin arm (p=0.68). As anticipated, patient satisfaction was significantly higher in the apixaban group than the enoxaparin group, 98.9% versus 58.8% (p<0.001).[88] Dabigatran was studied for extended prophylaxis in pancreatic cancer with similarly favorable safety and tolerability outcomes.[89]

We must consider the clinical significance of asymptomatic deep vein thrombosis, as identified in randomized clinical trials informing prolonged postoperative anticoagulation in the population with cancer. Screening for asymptomatic deep vein thrombosis is not routinely done, and the clinical implications of distal deep vein thrombosis on outcomes remain undefined. Furthermore, only 25% of untreated calf deep vein thromboses are expected to extend proximally.[90] In earlier studies, no difference in pulmonary embolism or mortality was identified when comparing conventional with extended thromboprophylaxis, suggesting that incidental deep vein thrombosis might not have clear clinical implications.[86] Conversely, the postoperative state is highly thrombogenic in patients with cancer, and

that asymptomatic deep vein thrombosis is of greater relevance is biologically plausible. Additionally, in a large autopsy study, only 106 of 260 patients with pulmonary embolism were found to have a definitive source, suggesting that asymptomatic deep vein thrombosis could pose a meaningful risk.[91] Ultimately, which characteristics of the surgery, the patient, or the underlying malignancy inform the risk of progression of asymptomatic deep vein thrombosis is unknown; and therefore, we recommend that patients with cancer undergoing surgical intervention receive extended prophylactic anticoagulation.

Guidelines

Recommendations from multiple professional organizations are summarized in table 4.

Emerging treatments

Monoclonal antibodies are being investigated as potential additional agents for the prevention of venous thromboembolism. These drugs work to inhibit and bind factor XI in its zymogen (inactive) form and thus prevent clot propagation. A recent randomized trial comparing this drug with enoxaparin in postoperative knee replacement patients showed potential efficacy.[92] Tissue pathway factor inhibitors such as recombinant anticoagulant protein 2C, derived from hookworms, have also showed promise in preventing deep vein thrombosis from acting directly on the coagulation cascade. Data also show that drugs used to treat other conditions such as asthma and hypercholesterolemia could also potentially be used to inhibit clot formation. Aptamers, which are short segments of single stranded DNA or RNA, are also being studied specifically to target clots and inhibit propagation.[93]

Conclusion

Venous thromboembolism remains a substantial cause of morbidity and mortality in patients with cancer. Several factors including tumor burden, venous stasis, and thrombocytosis are significant risk factors for the development of thrombosis, particularly in patients with cancer. People with certain malignancies, including gastric, hematological, and gynecological malignancies, are at particularly high risk for the development of venous thromboembolism. Several risk stratification tools are available to assess which patients are at highest risk and merit prophylactic intervention to mitigate the risk of venous thromboembolism. Surgical oncology patients undergoing cancer directed surgery, debulking, and removal of tumor are at particularly high risk of development of this VTE, and should undergo risk appropriate intervention to prevent harm with postoperative venous thromboembolism. Several new agents are available that obviate the difficulties of older strategies to prevent thrombosis in patients with cancer, and should be considered as preventive interventions.

Questions for future research

- What is the optimum duration of VTE prophylaxis in postoperative surgical oncology patients?
- Which patients are at the highest risk of developing VTE based on cancer type, both histological and anatomical?
- What novel agents can be used to treat cancer induced VTE and which limit side effect profiles such as bleeding and thrombocytopenia?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Patients were queried as part of the randomized control trial[88] on ease of undergoing postoperative anticoagulation after surgery for suspected malignancy. Questions included what issues prevent the use of anticoagulation in the oncological population.

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