

Primary prevention and treatment of venous thromboembolic events in patients with gastrointestinal cancers - Review

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Abstract

Venous thromboembolism event (VTE) is a common and morbid complication in cancer patients. Patients with gastrointestinal cancers often suffer from symptomatic or incidental splanchnic vein thrombosis, impaired liver function and/or thrombocytopenia. These characteristics require a thorough risk/benefit evaluation for individual patients. Considering the risk factors for the development of VTE and bleeding events in addition to recent study results may be helpful for correct initiation of primary pharmacological prevention and treatment of cancer-associated thrombosis (CAT), preferably with low molecular weight heparins (LMWH). Whereas thromboprophylaxis is most often recommended in hospitalized surgical and non-surgical patients with malignancy, there is less agreement as to its duration. With regard to ambulatory cancer patients, the lack of robust data results in low grade recommendations against routine use of anticoagulant drugs. Anticoagulation with LMWH for the first months is the evidence-based treatment for acute CAT, but duration of secondary prevention and the drug of choice are unclear. Based on published guidelines and literature, this review will focus on prevention and treatment strategies of VTE in patients with gastrointestinal cancers.

Key words: Thromboembolism; Gastrointestinal cancer; Prophylaxis; Treatment; Anticoagulation

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Core tip: The risk for venous thrombosis and pulmonary

embolism is clearly elevated in patients with gastrointestinal cancers. This risk is highest for patients with pancreatic, gastric or colorectal cancer and those receiving anti-cancer therapies. Available guidelines usually refer to thromboembolism in cancer patients without differentiating between types of cancer. Those patients with gastrointestinal cancers are more likely to present with additional problems such as hepatopathy-associated low platelet counts and/or prolonged prothrombin times. Furthermore, symptomatic or incidental thromboembolism of the visceral veins may occur more often. Identifying the risk factors for the development of venous thromboembolism and bleeding events may be helpful for correct initiation of primary pharmacological prevention and treatment of cancer-associated thromboembolism. Based on published guidelines and literature, this review will focus on prevention and treatment strategies of venous thromboembolism in patients with gastrointestinal cancers.

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INTRODUCTION

Venous thromboembolism (VTE) commonly presents as deep vein thrombosis (DVT) or pulmonary embolism (PE), occasionally as thrombosis of the hepatic, portal, or splanchnic veins. Patients with cancer are at increased risk for VTE^[1-4]. In addition to prothrombogenic cancer-related factors, the risk for symptomatic VTE is modulated by patient-specific and treatment-related factors (Table 1). Among the different subtypes of malignancy, some gastrointestinal cancers have a clinically relevant VTE incidence of more than 5% in the first year after cancer diagnosis (Figure 1), such as pancreatic (16%-22%), gastric (12%-17%) and colorectal (8%-12%) cancers^[2,5-8]. Symptomatic VTE is not only associated with substantial morbidity and complications in clinical management, but has been shown to have a detrimental effect on cancer survival^[9-11]. Acute and follow-up complications such as intestinal necrosis and esophageal bleeding due to portal hypertension may be life threatening if intra-abdominal veins are involved^[12-15].

Furthermore, anticoagulation with a vitamin K antagonist (VKA), such as warfarin, is complicated by drug interactions and variable drug absorption due to the changing nutritional status of cancer patients^[16]. In fact, therapeutic anticoagulation with VKA does not prevent VTE recurrences as effectively as in non-cancer patients, and major bleeding complications are also more than twice as common^[17]. Acute anticoagulation and secondary prevention with low molecular weight heparin (LMWH) has been established as an effective treatment

of VTE in cancer patients^[18], but daily subcutaneous application may result in local complications such as hematoma or infections, thus negatively influencing quality of life.

Most research into the primary prevention and treatment of VTE included both cancer and non-cancer patients. Recommendations for patients with malignancies are therefore based on the sparse available evidence and the guidelines differ only marginally (Table 2)^[19-27]. Most clinical studies focusing on VTE in cancer patients do not differentiate between different kinds of cancer, resulting in a lack of specific data concerning VTE in gastrointestinal cancers.

PERIOPERATIVE PROPHYLAXIS OF VTE IN CANCER PATIENTS UNDERGOING SURGERY

The risk for VTE is higher in cancer patients undergoing surgery without prophylaxis in comparison to non-cancer surgical patients^[27,28]. Administration of LMWH or fondaparinux (FPX) in these patients significantly reduces the rate of VTE^[29,30]. Dosages of LMWH in the range of 3000-5000 anti-FXa units per day are more effective than and as safe as lower doses. Patients undergoing major abdominal or pelvic surgery for malignancy remain at risk for VTE for up to five weeks after surgery. Thus, a prolonged pharmacologic thromboprophylaxis (LMWH or FPX once daily) should be considered, unless contraindicated because of high bleeding risk or active bleeding^[31,32]. Prophylactic regimens begin 12-24 h pre- or 6-24 h postoperatively^[29-32]. Based on these studies^[31-33], and according to the different guidelines (Table 2), antithrombotic prophylaxis is recommended for a minimum of 7 d and up to 35 d postoperatively. FPX (2.5 mg/d) was found to be as effective and safe in preventing VTE after abdominal surgery as the LMWH dalteparin (5000 antiFXa units/d). A post-hoc analysis of 1407 (out of 2048) patients with cancer demonstrated a significant (39%) risk reduction of VTE^[29]. Accordingly, the European (ESMO) guideline^[20] recommends extended prophylaxis for all patients undergoing elective cancer surgery. In the American guidelines (ASCO, NCCN)^[19,34], extended prophylaxis is only recommended in the presence of high thromboembolic risk factors such as residual or advanced cancer, aged 60 or older, obesity, previous history of VTE, duration of surgery longer than 2 h or prolonged postoperative immobilization. In patients with contraindications to pharmacological anticoagulant prevention strategies (*e.g.*, increased risk of hemorrhage), the use of intermittent pneumatic compression devices or compression stockings is advised^[19-27].

The recommendations for patients undergoing minimally invasive or laparoscopic surgery are even less evidence-based. In a recently published randomized study evaluating postoperative antithrombotic prophylaxis with LMWH for one vs four weeks in patients undergoing

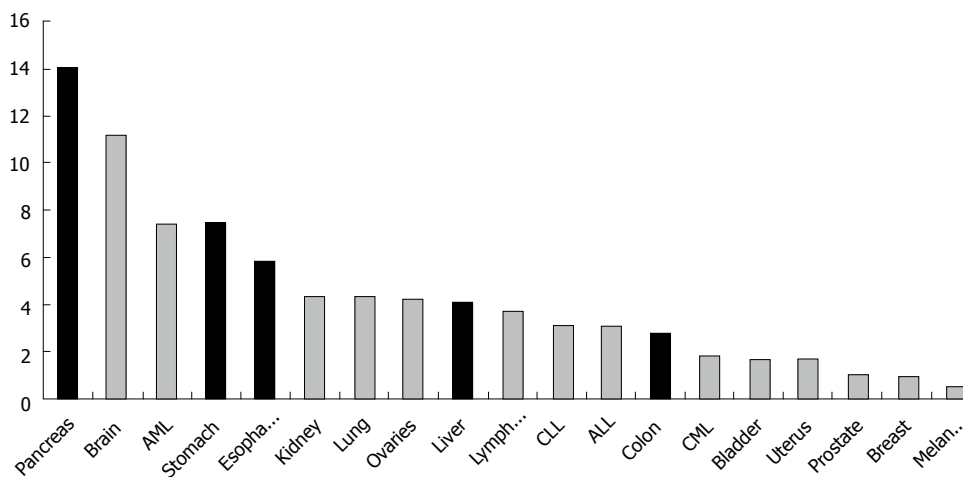


Figure 1 Venous thromboembolic event-risk according to different cancer entities (modified from Wun *et al*^[51] 2009). VTE-Incidence in the first year after cancer diagnosis (all stages) California Cancer Registry 1993-1999 (Patient Hospital Discharge Dataset). VTE: Venous thromboembolism event.

Table 1 Some venous thromboembolic event risk factors in cancer patients

Cancer-related	Patient-related	Treatment-related
Reduced mobility		
Primary cancer (e.g., pancreatic cancer > colo-rectal cancer)	Age	Operation
Stage (IV > III)	History of VTE	Chemotherapy
Histology (e.g., adeno- > squamous cell-carcinoma)	Infection/fever	Central line/port-catheter
Grade (3 > 2)		Parenteral nutrition
Thrombocytosis		Radiation therapy
Leukocytosis		
Acute phase (elevated CRP)		
Elevated D-dimer		

CRP: C-reactive protein; VTE: Venous thromboembolic event.

laparoscopic surgery for colorectal cancer, extended antithrombotic prophylaxis was safe and reduced the 3-mo risk of VTE by more than 90%, and that of proximal DVT by 50%, as compared to the one week regimen^[35]. These data are consistent with the suggestion to follow the same recommendations regardless of whether a cancer patient is to undergo an open or laparoscopic surgical intervention^[36,37].

Prevention of portal vein thrombosis

Splanchnic vein thromboses (SVT), including portal vein thrombosis (PVT), mesenteric vein thrombosis, splenic vein thrombosis and the Budd Chiari syndrome are frequent events in patients with hepato-biliary-pancreatic cancers, with cancer-associated PVT responsible for 21% of all cases^[14]. The risk of VTE and SVT is increased in patients with cirrhosis^[38,39], and PVT is a relevant complication of hepato-biliary-pancreatic surgery^[40], reported to occur in 9% of patients after liver resections^[41]. In this context, thromboprophylaxis with LMWH was demonstrated to be effective and safe in a retrospective comparative cohort study of 201 patients undergoing liver resections for liver cancers, with a reduction in PVT from 10% to 2%^[42]. These data suggest that prophylactic anticoagulation with

LMWH - as recommended in patients undergoing major abdominal cancer surgery - is also effective in cancer patients undergoing liver resection.

PROPHYLAXIS OF VTE IN HOSPITALIZED MEDICAL PATIENTS WITH CANCER

Hospitalized patients with active cancer - a term not uniformly defined - were included in all published randomized clinical trials investigating the role of unfractionated heparin (UFH), LMWH or FPX for the prevention of VTE. Treatment of hospitalized patients for 6-14 d with low-dose enoxaparin (20 mg/d s.c.) was ineffective^[43], whereas higher prophylactic doses of LMWH (enoxaparin 40 mg/d, or dalteparin 5000 anti FXa units/d)^[43,44] or FPX (2.5 mg/d)^[45] demonstrated superiority compared to placebo in the prevention of VTE with minimal or no increase in major bleeding events. Subgroup analyses failed to identify a subgroup which did not benefit from pharmacological thromboprophylaxis^[46]. This was also true for a small subgroup (5%-15% of the study population) of cancer patients.

Subgroup analysis of 274 patients with active cancer from the CERTIFY study comparing UFH (3 × 5000 IU/d) with LMWH (certoparin 3000 anti FXa units/d) demonstrated a similar VTE risk (5.3% vs 4.1%) and similar rates of any (4.0 vs 3.9) or major (0.7% vs 0.5%) bleeding compared to the 2965 patients without cancer^[47,48].

Based on three studies, extended prophylaxis with the anticoagulant drugs LMWH^[49] or non-vitamin K oral anticoagulant drugs (NOACs)^[50,51] cannot be recommended in medical patients. In the MAGELLAN trial^[51], cancer patients (n = 592; 7.3%) had higher rates of VTE when prophylaxis with rivaroxaban was extended from 10 to 35 d.

Discussion is ongoing as to whether all cancer patients hospitalized for reasons such as infectious complications or complex chemotherapy regimens should generally receive medical thromboprophylaxis unless contraindicated by active bleeding or high bleeding risk^[52-55]. According to the

Table 2 Comprehensive outline of some guidelines focusing on the prevention and treatment of cancer associated venous thromboembolism

	Primary prophylaxis/prevention of VTE in cancer patients			Treatment of cancer-associated VTE	
	Surgical patients	In-patients (non surgical)	Out-patients	Acute/initial	Long-term/secondary prevention
ASCO Guidelines 2013 ^[15]	UFH, LMWH (Dalteparin, Enoxaparin), Fondaparinux A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest risk patients. Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 d and it should be considered an extension up to 4 wk in patients undergoing abdominal and pelvic surgery	UFH, LMWH (Dalteparin, Enoxaparin), Fondaparinux	Not recommended routinely ¹ LMWH may be considered	UFH, LMWH (Dalteparin, Enoxaparin, Tinzaparin), Fondaparinux VKA not recommended	LMWH (Dalteparin, Enoxaparin, Tinzaparin) VKA (INR 2-3) acceptable if LMWH is not available Use of NOACs is not recommended Treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation
ESMO Guidelines 2011 ^[16]	LMWH (Dalteparin, Enoxaparin), UFH Fondaparinux not recommended Cancer patients undergoing elective major abdominal or pelvic surgery should receive in hospital and post-discharge prophylaxis with s.c. LMWH for up to 1 mo after surgery	LMWH (Dalteparin, Enoxaparin), Fondaparinux, UFH	Not recommended routinely May be considered in high risk patients	LMWH (Enoxaparin, Dalteparin), UFH	Treatment for a total of 6 mo. Initial dose of LMWH 100% for 1 mo, thereafter 5 mo with 75%-80% of the initial dose of LMWH
International Consensus Groupe 2013 ^[17]	LMWH (Dalteparin, Enoxaparin, Nadroparin, Tinzaparin), Fondaparinux, UFH For 10 ± 2 d or 25-31 d (28 d) extended use (Bemiparin sodium 3500 IU per day for 28 d)	LMWH (Dalteparin, Enoxaparin, Nadroparin, Tinzaparin), Fondaparinux, UFH	Not recommended routinely To be considered/ recommended: Patients with locally advanced or metastatic lung or pancreatic cancer treated with chemotherapy and having a low bleeding risk	LMWH (Dalteparin, Enoxaparin), UFH	LMWH (Dalteparin, Enoxaparin) for 3 to 6 mo
British Committee for Standards in Haematology 2015 ^[18]	Patients undergoing abdominal and pelvic surgery for cancer should be considered for extended thromboprophylaxis	Patients with active or recent cancer should receive thromboprophylaxis throughout their admission unless contraindicated Patients without a history of venous thromboembolism receiving adjuvant hormonal therapies for cancer should not routinely receive thromboprophylaxis	Patients should be assessed for thrombosis risk and although most do not routinely require thromboprophylaxis, it should be considered for high risk patients	Initial treatment should be with LMWH for six months Cancer patients with incidental pulmonary embolus or deep vein thrombosis should be therapeutically anticoagulated as for symptomatic disease	Warfarin and other oral anticoagulants are acceptable alternatives if LMWH is impractical and anticoagulation is indicated Anticoagulation should be continued, taking pt status and wishes and bleeding risk into consideration. There is a rationale but little direct evidence for preferring to continue to use LMWH

Australian Governments National Health and Medical Research Council 2009 ^[19]	LMWH, continue for at least 7 to 10 d following major general surgery Consider using extended thromboprophylaxis with LMWH for up to 28 d after major abdominal or pelvic surgery for cancer, especially in patients who are obese, slow to mobilise or have a past history of VTE	LMWH, UFH	-	-	
MAYO CLINIC VTE Prevention and Management Guidelines 2014 ^[20]	UFH, LMWH (Enoxaparin, Dalteparin), Fondaparinux Cancer patients undergoing pelvic or abdominal surgery should receive 4 wk of LMWH	UFH, LMWH (Enoxaparin, Dalteparin), Fondaparinux	UFH, LMWH (Enoxaparin, Dalteparin), Fondaparinux VKA (INR2-3)		Anticoagulants are continued until there is no evidence of active malignant disease defined as any evidence of cancer on cross-sectional imaging or any cancer-related treatment (surgery, radiation, or chemotherapy) within the past 6 mo
ASH Guidelines 2013 ^[21]	UFH, LMWH, Fondaparinux in all patients undergoing major surgical intervention for malignant disease Prolonged prophylaxis for up to 4 wk may be considered in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features such as residual malignant disease, obesity, and prior history of VTE	UFH, LMWH, Fondaparinux	Routine VTE prophylaxis in ambulatory patients receiving chemotherapy is not recommended	LMWH	LMWH Continue treatment with LMWH is preferred for at least the initial 6 mo of treatment
German Guidelines ^[22,23]	LMWH, Fondaparinux, (UFH) Patients undergoing abdominal and pelvic surgery for cancer are recommended to get extended thromboprophylaxis (28 to 35 d)	LMWH, Fondaparinux, (UFH)	LMWH, Patients should be assessed for thrombosis risk and thromboprophylaxis should be considered for high risk patients	LMWH, Fondaparinux, UFH	LMWH for 3 to 6 mo If cancer persists extended secondary prophylaxis (with LMWH, VKA, or NOAC) is useful (till death)

¹For highly selected high-risk patients (e.g., such as those with pancreatic cancer) preventive anticoagulation may be considered to be applied routinely. VTE: Venous thromboembolic event; LMWH: Low molecular weight heparins; UFH: Unfractionated heparin; VKA: Vitamin K antagonist; INR: International normalized ratios; NOAC: New oral anticoagulants.

available guidelines (Table 2), routine thromboprophylaxis should at least be considered. Italian investigators assessing the risk of VTE in hospitalized medical patients confirmed cancer to be a major predisposing factor for VTE (PADUA prediction score), without differentiating between cancers^[56]. However, the existence of active cancer on its own does not classify as a high VTE risk unless additional risk factors are present (Table 1).

VTE PROPHYLAXIS IN OUTPATIENTS WITH CANCER

Prevention of catheter-related VTE

Patients who have been recently diagnosed with cancer are at high risk for VTE^[57,58]. Nowadays these patients usually receive non-surgical therapies such as

radiation, chemotherapy or radiochemotherapy in an outpatient setting. Long-term central venous catheters (e.g., port or picc line catheters) are used to facilitate drug administration in many of these patients. There is an increased risk of DVT in the subclavian or jugularis interna veins after insertion of a central line, with an estimated incidence of asymptomatic catheter-related DVT of about 20%, although less than 5% develop clinical symptoms, which very rarely result in symptomatic PE or relevant post-thrombotic sequelae^[59-64]. Multicenter randomized double blind placebo-controlled studies to assess the efficacy and safety of LMWH or VKA demonstrated a significant reduction in asymptomatic catheter-related thrombi, but failed to show significant benefit with regard to clinically symptomatic DVT^[59]. International guidelines therefore recommend against routine prophylaxis for this

Table 3 Primary prevention of cancer-associated venous thromboembolic event in gastrointestinal cancers

Study	Cancer	n	VTE placebo	VTE LMWH	VTE U-LMWH	RR
PROTECHT ¹	Gastrointestinal ²	148/272	2.7%	1.5%		-44%
Agnelli <i>et al</i> ^[68] , 2009	Pancreas	17/36	5.9%	8.3%		40%
SAVE-ONCO	Colo-rectal	461/464	2.0%		1.1%	-45%
Agnelli <i>et al</i> ^[69] , 2012	Pancreas	128/126	10.9%		2.4%	-78%
	Stomach	207/204	1.9%		0.5%	-75%
FRAGEM	Pancreas	60/63	23%	3.4%		-85%
Maraveyas <i>et al</i> ^[70] , 2012						
CONKO 004	Pancreas	152/160	9.9%	1.3%		-87%
Pelzer <i>et al</i> ^[71] , 2015						

¹Randomization 1:2; ²Gastric ($n = 40/58$), colon ($n = 79/156$) and rectal ($n = 29/58$) cancers. LMWH: Low molecular weight heparin; U-LMWH: Ultra-LMWH; RR: Relative risk; VTE: Venous thromboembolic event.

indication.

Antithrombotic prophylaxis in cancer outpatients receiving chemotherapy

The risk of VTE in cancer patients is especially high during the first weeks or months of specific therapy^[4,62,65]. Several clinical trials have evaluated the role of primary prevention in outpatients with selected or unselected malignancies. An early study on patients receiving chemotherapy for advanced breast cancer found low dose warfarin to be safe and efficacious, with 85% relative reduction in VTE compared to placebo^[66]. Two other randomized trials in patients with breast or lung cancers using prophylactic dosages of LMWH failed to show a benefit^[67]. The PROTECHT study, however, showed a statistically significant relative risk reduction of 50% for symptomatic VTE in cancer outpatients receiving chemotherapy for different types of malignancy (including gastrointestinal cancers) in favor of prophylactic dosages of the LMWH nadroparin (Table 3)^[68]. Moreover, despite a relatively low event rate of less than 3% in the placebo group, prophylactic dosages of semuloparin, an ultralow molecular weight heparin (not further developed), demonstrated a highly significant reduction (65%) of VTE in patients with metastatic or locally advanced solid cancers (1590 of 3212 with pancreatic, gastric or colorectal cancers) receiving chemotherapy^[69] (Table 3), without an increase in the incidence of clinically relevant or major bleeding complications. Whereas these trials investigated the effect of prophylactic dosages of antithrombotic drugs, two randomized open-label studies in patients with advanced pancreatic cancer undergoing chemotherapy investigated primary prophylaxis with higher doses of LMWH (Table 3). The phase II FRAGEM-trial^[70] examined the therapeutic dose of dalteparin (200 anti FXa units/kg per day), and the phase III CONKO-004 trial^[71] used half the therapeutic dosage of the LMWH enoxaparin (1 mg/kg per day). Despite differences in study design and primary endpoint of effectiveness, both trials found this intensity of anticoagulation to be safe and reported a more than 80% relative risk reduction of thromboembolic events compared to observation (Table 3).

Nevertheless, available international guidelines do

not recommend routine prophylaxis in all ambulatory cancer patients receiving anti-cancer chemotherapy (Table 2). ACCP and ASCO guidelines^[19,62] suggest considering antithrombotic prophylaxis in outpatients receiving chemotherapy with unspecified solid tumors and additional risk factors, whereas others recommend considering primary prevention, especially in patients with lung or pancreatic cancer^[21] in accordance with a recent meta-analysis^[72].

A number of attempts have been made to classify individual cancer outpatients receiving chemotherapy more precisely according to VTE risk. In this context, the scoring system developed by Khorana *et al*^[73] (Table 4), which associates pancreatic and stomach cancer with a very high VTE risk, demonstrated potential for the identification of cancer outpatients at risk for VTE prior to the start of chemotherapy with simple and commonly available criteria. A prospective randomized trial investigating the benefit of primary antithrombotic prophylaxis in high risk patients according to this score is ongoing. Until results from this study become available, the initiation of pharmacological prophylaxis in high risk patients is suggested by the standardization subcommittee of the ISTH^[74]. Supplementing the Khorana score with lab parameters such as D-dimer and soluble P-selectine^[75] or chemotherapy components such as gemcitabine and cis- or carboplatin^[76] may further categorize patients according to their VTE risk.

With the exception of patients suffering from pancreatic cancer, for whom primary prophylaxis with LMWH is highly warranted unless contraindicated by increased bleeding risk, insufficient evidence is available regarding other gastrointestinal cancers to recommend routine primary prevention with anticoagulant drugs. Until further evidence has accumulated, the Khorana score is helpful for classification of patients with gastrointestinal cancer according to their VTE risk and as an aid in decision-making regarding initiation of pharmacologic prophylaxis. While prophylactic dosages of LMWH may be effective in most gastrointestinal cancers, half-therapeutic dosages of LMWH should be considered for patients with advanced pancreatic cancer in the first three months of chemotherapy.

Table 4 Assessment scores for prediction of the venous thromboembolic event-risk in cancer out-patients receiving chemotherapy, according to Khorana *et al.*^[73], Pabinger *et al.*^[75] and Verso *et al.*^[76]

Khorana score criteria ^[73]	Score
Primary cancer	
With very high risk (pancreas, stomach) (high grade glioma ¹)	2
With high risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Platelet count prior to chemotherapy > 350000/ μ L	1
Hb < 10 g/dL or ESA-application	1
Leukocyte count prior to chemotherapy > 11000/ μ L	1
Body mass index > 35 kg/m ²	1
High risk	> 3
Vienna prediction score (additional parameters to Khorana score) ^[75]	
D-dimer > 1.44 μ g/mL	1
Soluble P-selectin > 153.1 μ g/mL	1
High risk	> 4
Protecht prediction score (additional parameters to Khorana score) ^[76]	
Cisplatin or carboplatin	1
Gemcitabine	1
High risk	> 3

¹High grade glioma are considered very high risk site of cancer in the Vienna prediction score only. ESA: Erythropoiesis stimulating agents.

VTE risk and new drugs

The introduction of new drugs which target angiogenesis, tumor stroma or immunity in gastrointestinal cancer medicine led to the realization that individual VTE risk may be strongly influenced by the drugs. For example, the introduction of bevacizumab for the treatment of advanced colorectal cancer not only resulted in a clinically relevant increase in bleeding, but in thromboembolic complications as well^[75,77,78].

Moreover, drug-associated VTE may become an important factor limiting further cancer therapy development. At the ASCO meeting in May 2015, Hingorani *et al.*^[79] presented a phase II trial in pancreatic cancer patients treated with gemcitabine, nab-paclitaxel and recombinant pegylated hyaluronidase - an experimental drug - which had to be stopped due to high numbers of VTEs. A prophylactic dose of LMWH (40 mg enoxaparin/d) was not effective, but the use of half therapeutic doses of enoxaparin (1 mg enoxaparin/kg per day) allowed the continuation of the study.

TREATMENT OF ACUTE VTE IN CANCER PATIENTS

The treatment of patients with active cancer and acute VTE with the standard treatment for non-cancer VTE patients (LMWH or FPX plus concurrent introduction of anticoagulation with VKA) resulted in a two- to three-fold increase of both re-thrombosis and bleeding^[17,18]. Several randomized controlled trials compared prolonged application of LMWH to oral anticoagulation with VKA in patients with cancer-associated thrombosis (CAT) and demonstrated superior efficacy of LMWH with no increase

in bleeding complications (Table 5), results confirmed by meta-analysis^[18,19,80,81]. Based on these results, guidelines recommend a standard treatment of three to six months of weight-adjusted LMWH regardless of whether the patient suffers from gastrointestinal or another type of cancer (Table 2). The underlying malignancy, probably representing the most important risk factor for VTE, continues beyond six months after the initial VTE in most of these patients. Therefore, anticoagulation beyond this period may be warranted and is recommended in most guidelines (Table 2). Nevertheless, evidence for this recommendation is clearly weaker, as prospective randomized trials investigating type of anticoagulation, dosage of anticoagulant drugs or duration of prolonged anticoagulation have not been reported. Available data suggest that the pro-thrombotic risk correlates with disease progression due to increasing tumor load, decreasing performance status, progressive mobility reduction and increased use of palliative chemotherapy^[82-84]. On the other hand, an increased bleeding risk, associated with progression of cancer, prolonged anticoagulation and prolonged chemotherapy needs to be considered in order to balance the benefit of preventing recurrent VTE against the risk of bleeding^[83,84]. Furthermore, the impact of prolonged anticoagulation on the quality of life of cancer patients needs to be considered.

Although clinical guidelines (Table 2) currently recommend considering indefinite anticoagulation in patients with advanced malignancy, they do not recommend a specific anticoagulant drug due to the limited evidence available.

Treatment of acute PVT

Acute thrombosis of splanchnic veins - PVT in particular - is a frequent complication in patients with cancers of the hepato-biliary-pancreatic system^[23,85]. PVT results in portal hypertension and impairment of liver perfusion. Spread of thrombosis to splenic or mesenteric veins can result in fatal complications such as splenic or intestinal infarction. Anticoagulation is the therapy of choice in non-cirrhotic, non-cancer patients, with successful recanalization in about half of acute PVT cases^[86,87]. Anticoagulation is considered in patients with cirrhosis and PVT with a small increase in bleeding complications^[86], and can safely be combined with placement of transjugular intrahepatic portosystemic shunts^[87]. Unfortunately cancer patients, *e.g.*, those with gastrointestinal cancers, were excluded from these trials^[86,87].

Treatment of cancer-associated PVT is therefore based on evidence from non-cancer patients with or without cirrhosis. Despite the fact that prophylactic and therapeutic anticoagulation seems to be effective and safe for cirrhotic patients^[86-88], an individual risk/benefit evaluation which takes prognosis, anticancer treatment options and acute anticoagulation-associated bleeding risk, as well as future complications with the associated consequences for surgical interventions and the risk of variceal hemorrhage into consideration is challenging.

Table 5 The CLOT and CATCH studies^[80,81]: Study-population characteristics and study outcomes

	CLOT	CATCH	VKA	Dalteparin	P	VKA	Tinzaparin	P
Study-population characteristics								
<i>n</i>	676	900						
Women	52%	59%						
Median age (yr)	63	59						
ECOG 0-1	63%	77%						
Metastasized cancer	67%	55%						
Brest cancer	17.6%	9%						
Colo-rectal cancer	17.8%	13%						
Lung cancer	14.8%	12%						
Gynecological cancer	11.2%	23%						
Pancreatic cancer	4.8%							
Urogenital cancers	14.2%							
Brain cancers	5.5%							
Hematological cancers	10%	10%						
Study outcomes								
VTE			15.8%	8.0%	0.002	10.0%	6.9%	0.07
DVT			11.0%	4.2%		5.3	2.7	0.04
Fatal PE			2.1%	1.7%		3.8%	3.8%	
Non-fatal PE			2.7%	2.7%		0.7%	0.4%	
Major bleeding			4%	6%	0.25	2.7%	2.9%	
CRNM-bleeding						16%	11%	0.03
Any bleeding			19%	14%	0.09			
6-mo mortality			41%	39%		41%	40%	
INR < 2			30%			26%		
INR 2-3			46%			47%		

VKA: Vitamin K antagonist; VTE: Venous thromboembolic event; DVT: Deep vein thrombosis; PE: Pulmonary embolism; INR: International normalized ratios.

Treatment of CAT in particular situations

Thrombocytopenia is a well-known effect of chemotherapy in cancer patients and higher degrees of thrombocytopenia increase the risk of hemorrhage. Anticoagulation should therefore be administered to thrombocytopenic patients after thorough evaluation of the risks and benefits. The risk of recurrent VTE is high in the month following the initial diagnosis on beginning cancer therapy^[1,4]. Full therapeutic anticoagulation with LMWH is considered appropriate in these situations when the platelet count is above 50000/ μ L, and a reduction of anticoagulation intensity to 75% or even 50% may be reasonable later in the course of treatment. When platelets are below 50000/ μ L but above 20000/ μ L, a half-therapeutic to prophylactic dose should be considered^[89].

It should be recognized that increased prothrombin times and elevated international normalized ratios (INR) as a result of hepatic dysfunction only reflect reduced synthesis of coagulation factors. In fact coagulation inhibitors are also decreased, resulting in a well-balanced but more labile equilibrium with normal thrombin generation capacity^[90,91]. For this reason patients with reduced hepatic capability are not protected against VTE, despite an increased INR, but patients with cancer and hepatic dysfunction have an increased VTE risk^[90,92]. Again, higher grade evidence in favor of or against full-dose anticoagulation in patients with CAT and reduced liver function due to pre-existing cirrhosis or advanced hepatic metastasis resulting in increased INR is lacking. Clinical experience suggests a cautiously balanced approach of 75% to 100% of the therapeutic LMWH

anticoagulation dose for acute VTE.

VTE recurrences are to be expected in more than 5% of patients within the first months despite CAT therapy according to guidelines with LMWH (Table 5). Again, there is sparse evidence on treatment of these patients. Based on a report from Carrier *et al.*^[93], a 20% increase in LMWH dose - without adjustment to laboratory parameters - is a practical, safe and effective approach.

NON-VITAMIN-K ANTAGONIST ORAL ANTICOAGULANTS IN THE PREVENTION OR TREATMENT OF CAT

A number of new oral anticoagulants (NOAC) have been introduced and licensed for prevention and treatment of VTE in recent years^[94]. These drugs work by direct inhibition of active coagulation factors direct oral anti-coagulants (DOAC), namely factor IIa/thrombin (dabigatran) or factor Xa (apixaban, edoxaban, rivaroxaban). The term non-vitamin K oral anticoagulant was created in order to maintain the acronym NOAC. Although these drugs have been successfully tested and licensed in trials investigating NOACs in the post-operative setting of elective hip or knee replacement, drug development for other surgical patients was never initiated and the programs for medical patients were stopped early^[50,51]. A placebo-controlled dose-finding phase II trial for primary prophylaxis of VTE in ambulatory cancer patients undergoing chemotherapy showed relevant activity^[95], but this indication has not yet been further developed. There

Table 6 Take home messages

<p>Patients with gastrointestinal cancers are among those with the highest cancer-associated VTE risk (<i>e.g.</i>, pancreatic cancer, gastric cancer)</p> <p>Primary prevention of VTE should be considered according to an individual risk-benefit estimation</p> <p>Scoring systems help to identify patients at high VTE risk. These patients may benefit from prophylactic anticoagulation</p> <p>Usual prophylactic dosages of LMWH may not be effective enough in patients with the highest risk (<i>e.g.</i>, pancreatic cancer)</p> <p>Gastrointestinal cancer patients with VTE should have medical anticoagulation therapy with LMWH for at least three to six months</p> <p>In patients with gastrointestinal cancers splanchnic vein thrombosis, portal hypertension, hepatopathy-associated coagulation defects (<i>e.g.</i>, decreased prothrombin time) and thrombocytopenia may complicate anticoagulation strategies</p>
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VTE: Venous thromboembolic event; LMWH: Low molecular weight heparins.

is therefore no evidence for the use of NOACs for primary prevention in hospitalized or ambulatory cancer patients undergoing surgery or any other kind of anticancer therapy.

The four drugs mentioned above have all been compared to VKA (warfarin) in randomized phase III trials for the treatment of DVT, PE and atrial fibrillation^[96-101]. All of these trials demonstrated that NOACs are at least as effective and safe as VKA. As confirmed by meta-analysis, the study data for these NOACs showed a clinically relevant reduction in bleeding, most pronounced for intracerebral bleeding events^[102]. Depending on the inclusion and exclusion criteria of the individual studies and on the definition of "patients with active cancer", all six trials included cancer patients, a subgroup adding up to 2.5% of more than 25000 patients^[102]. Meta-analysis of these patients suggests a potential role for NOACs in patients with CAT, with a similar risk/benefit relationship as demonstrated in non-cancer patients^[76]. There are major drawbacks to the use of NOACs for this indication, however. First of all, standard therapy of CAT is LMWH for several months and not LMWH followed by VKA - the standard treatment arm in the VTE trials. Secondly, "patients with active cancer" included in the phase III trials demonstrate a three-month-mortality of less than 15%^[103-105], whereas those included in the two pivotal CAT trials (CLOT, CATCH) recruiting cancer patients ten years apart, have a six-month-mortality of 40%^[80,81] (Table 5). Obviously these patient groups differ to a great extent. Thirdly, despite having less interactions with other drugs compared to VKA, NOAC still bear a largely unclear risk of interactions with cytotoxic or targeted drugs. A CLOT- or CATCH-like head to head comparison of NOACs vs LMWH, the current standard of care, is eagerly awaited, especially as the oral application of NOACs might provide an improvement in quality of life compared to s.c. administered LMWH. Unless study data are available, NOACs are not to be considered the first choice in patients with acute CAT. As an alternative to LMWH or VKA (Table 2), anticoagulant treatment with NOACs beyond six months may be reasonable in many CAT patients, as there are no studies defining the optimal drug in this period.

CONCLUSION

The risk for VTE is clearly elevated in patients with (gastrointestinal) cancer. This risk is highest for patients

with pancreatic cancer and those receiving anti-cancer therapies. VTE is the second leading cause of death in patients with cancer, and mortality is increased among patients with CAT^[10,106]. Whereas available guidelines usually refer to VTE in cancer patients without differentiating between types of cancer, those with gastrointestinal cancers are more likely to present with additional problems such as hepatopathy-associated low platelet counts and/or prolonged prothrombin times. Furthermore, symptomatic or incidental VTEs of the visceral veins may occur more often. Despite limited data, prophylactic anticoagulation must be endorsed in most hospitalized patients with malignancies. In ambulatory patients undergoing chemotherapy, an assessment of individual prothrombotic and prohemorrhagic factors may help transfer the beneficial effect of pharmacologic prophylaxis demonstrated in a number of trials to those patients with the highest VTE risk, in particular those suffering from pancreatic cancer. Treatment recommendations for CAT with LMWH have been reconfirmed by recent evidence. Further progress will help clarify the risk/benefit relationship of NOACs in this field, identifying economic and quality of life aspects as well (Table 6).

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