Preventing Thrombosis in Cancer Patients

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ABSTRACT

Thromboembolism events, either venous (VTE) or arterial thromboembolism (ATE) remain a highly prevalent complication in cancer patients. Thrombosis is a leading cause of death, contributor to significant morbidity, the reason of delayed cancer treatment, leading to increased cancer financing and expenses. Both cancer and its treatment are recently found to be related to vascular inflammation through the induction of tissue factor (TF) expression and promoting a procoagulant state which triggers the activation of coagulation system. Several risk factors may also coexist such as dehydration, immobilization, smoking, obesity, previous DVT, etc. Even in patients with asymptomatic deep vein thrombosis (DVT), they have a three-fold increase in mortality. The high morbidity and mortality of VTE raises the need for thromboprophylaxis to reduce the incidence of overt thrombosis, albeit against its possible side effects related to anticoagulant prescription. This article highlighted the clinical perspectives for thromboprophylaxis while counting on the risk stratification in a particular cancer patient.

Keywords*: thrombosis, cancer, inflammation, thromboprophylaxis.*

INTRODUCTION

Cancer is a chronic disease with a high morbidity and mortality rate despite treatment advances. However, today many patients can survive longer due to progress in early diagnosis and progress in its treatment.[1] Cancer has long been known to be related to thrombosis and patients are reported to have a 7-fold increased probability compared to the general population.[2] Studies reported that the incidence of thrombosis in patients with cancer has been increasing overtime, partly due to its increasing incidence in recent years.[3] Therefore, management of complications especially thrombosis during the disease course are becoming more clinically relevant. Optimal strategies to manage cancer-associated thrombosis remains a major concern that challenges clinicians in daily clinical practice; due to the fact that thrombosis is a preventable complication.[3,4]

Venous and arterial thrombosis are the already known two spectrums of thrombosis.[4] Venous thromboembolism (VTE) represents a clinical condition whether the thrombus is developed in the venous vasculature of the lower extremities and pelvic veins, as well as visceral or splanchnic vein thrombosis. Thrombus migration proximally can travel along the bloodstream.

Pulmonary embolism (PE) can unexpectedly develop when the thrombus embolization occurs in the pulmonary artery or its branches which is the major cause of morbidity and mortality in patients with DVT.[5] In addition to VTE, arterial thromboembolism (ATE), including the myocardial infarction (MCI), cerebrovascular accident (CVA), and peripheral arterial disease (PAD) are also prevalent in patients with active cancer compared to non-cancer population.[4] Thrombosis events, either VTE or ATE, are the second-leading cause of mortality after cancer progression itself.[6,7] This make cancer-associated thrombosis a clinical conditions in which relevance should be increasingly recognized both for physician and medical oncologists.

This article aims to described the need for thromboprophylaxis treatment in cancer patients and how to identify those who would benefit, irrespective of the risks. The dogma that "prevention is better than cure" is not an exaggeration in terms of reducing the burden of thrombosis. The decision to prescribe anticoagulants as a prophylactic measure should be based on the risks of morbidity and mortality related to VTE/ATE, thrombosis recurrence, anticoagulant-related bleeding, as well as on social values and patient preferences, particularly in Indonesia.

THE BURDEN OF VTE (AND ATE) IN ONCOLOGICAL PRACTICE

Cancer patients will experience complications during the course of their disease, which includes disease progression, infections, side effects of chemotherapy, as well as thrombosis, which is a frequently occurring complication among others.[6,8] To weigh the benefits against the risks of thromboprophylaxis, clinicians need to be familiar with the burden of thrombosis in cancer patients (**Table 1**). The decision to provide thromboprophylaxis should be based on careful assessment of the benefits, such as reduction in VTE and possible arterial thromboembolism, against its harms including the side effect of bleeding from anticoagulant.[7] The risk of thrombosis in cancer patients, the purpose of anticoagulation, and the consequences in this population underlines the need for clinicians to carefully assess all factors before deciding to recommend any thromboprophylactic strategies.[9,10]

Thrombosis in cancer patients can ultimately interfere with cancer treatment, reduce the quality of life, lead to additional diagnostic tests, increase treatment cost, and prolong length of stay. Patients with a history of VTE have a higher risk of recurring thrombosis and an increased mortality rate.[7,11] Approximately 95% of blood clots originate from the proximal portion of the lower extremities. However, pulmonary embolism may also occur without prior DVT. Thrombosis can occur without the presence of any symptoms, referred to as incidental thrombosis. A study conducted in Dr. Kariadi Hospital reported the incidence of asymptomatic DVT to be 25.6% among cancer patients. Without prophylaxis, PE or even fatal PE can be the initial manifestation of VTE. Despite that, thrombotic events in cancer patients has not gained enough attention as seen by the lack of practice of thromboprophylactic use in clinical practice, although the international[4,5] and Indonesian national guidelines have been published since 2018.[12]

Table 1. Thromboprophylaxis and dire consequences of thrombosis in cancer patients.

Ultimate goals for thromboprophylaxis	
Prevent thrombosis	
Reduced risk of thrombosis recurrences	
Short-term (immediate) consequences	**Long-term consequences**
Morbidity caused by DVT and/or PE	Post-thrombotic syndrome
Interruption of cancer treatment	Chronic thromboembolic pulmonary hypertension
Reduced quality of life	Long-term bleeding risk
Financial consequences	
Increased mortality	

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism
Source: Mulder FI, *et al*. Cancers 2020, with modifications.

EPIDEMIOLOGY

Horsted et al.[13] reported that the incidence rates of venous thrombosis in cancer patients could be stratified by the background risk of VTE. The incidence among cohorts with average-risk patients was estimated to be 13 per 1,000 person-years (95% CI: 7-23). Among cohorts with high-risk characteristics, the overall incidence rate was incredibly high with 68 per 1,000 person-years (95% CI: 48-96). In terms of the type of cancer, certain cancer can interestingly be more hypercoagulable than others, such as those in the gastrointestinal tract, including gastric, esophageal, and pancreatic cancers (**Table 2**). Patients with brain and lung cancers also showed an increased risk of VTE by more than ten-fold compared to the general population.[14]

Table 2. Incidence of VTE among various types of cancer.

Type of cancer	First VTE per 100 person-years (95% CI)
Bladder	2.7 (2.4-3.0)
Breast	3.2 (2.9-3.4)
Prostate	4.4 (4.0-4.7)
Hematologic	4.5 (4.1-4.8)
Colon	6.7 (6.3-7.2)
Lung	10.1 (9.5-10.8)
Stomach	10.8 (9.5-12.3)
Ovary	11.9 (10.6-13.2)
Brain	12.1 (10.3-14.0)
Pancreas	14.6 (12.9-16.5)

Source: Cohen AT, *et al*. *Thromb Haemost* 2017.

Cancer patients have a 4- to 7-fold risk of developing VTE compared to non-cancer patients. According to Iorga et al.,[15] the prevalence of VTE in patients with cancer was 15% and correlated with poor treatment outcomes. Moreover, 20-30% of all VTE cases occurrs in cancer patients.[15,16] Data from a cohort study of 21,002 inpatients in California showed that 20% (4,368 patients) of cancer patients were found to have thrombosis.[16] A study in Korea reported that the cumulative incidence of VTE in 2 years has increased to 24.4% in patients with metastatic gastric cancer.[17] A retrospective cohort study conducted in Dharmais Cancer Hospital Jakarta showed that chemotherapy is a risk factor of DVT in patients with cancer (OR 5.0, p= 0.012).[18]

The risk of thrombosis can vary depending on the disease status. It generally increases during periods of active disease, hospitalization, tumor-directed therapy, and decreases during remission.[19,20] Chew *et al*. also reported an increased risk of VTE in all types of cancer with advanced metastasis.[21] The early phases following initial diagnosis is the period with the highest risk of developing VTE (**Figure 1**), where some prothrombotic mechanisms are involved in the CAT mechanism. The incidence of VTE is also high in patients undergoing chemotherapy. Cases of VTE in cancer patients is not limited to DVT and PE, but also thrombosis in unusual sites, such as the upper extremities, cerebral veins, and splanchnic veins.[22]

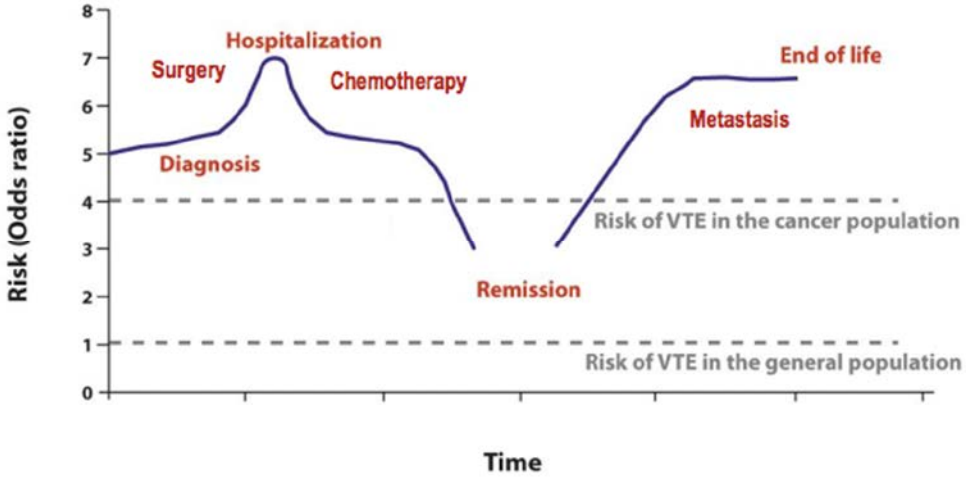

Figure 1. Dynamic changes in the risk of VTE along the course of cancer.
Reproduced with permission from Streiff MB. *Clin Adv Hematol Oncol* 2013.

RISK FACTORS FOR THROMBOSIS

The risk factors for thromboembolism are divided into patient characteristic risks, tumor-related risks, and therapy-related risks.[22] Thrombosis events in cancer patients are generally based on the interactions of each risk factor (**Table 3**). A person with more risk factors had a greater chance of developing thrombosis. Certain types of cancer have a higher incidence of thrombosis. This risk is also higher in the later stage of cancer and metastatic disease. As a concrete example, 60-70% of patients with pancreatic cancer has VTE as found in autopsy.[23]

PATHOPHYSIOLOGY OF THROMBOSIS IN CANCER PATIENTS

On the basis of thrombosis, there is the so-called Virchow's triad of endothelial injury, hypercoagulability, and venous stasis. Cancer cells can activate coagulation pathways by direct and indirect mechanisms. The direct mechanism involves production of procoagulant factors, such as tissue factors, which is constitutively expressed by cancer cells that bind to circulating FVIII and activate coagulation pathways. The indirect mechanism involves an exposure of proinflammatory cytokine stimulation in the tumor microenvironment,[24] and the administration of chemotherapy also causes damage to endothelial cells, therefore triggering an inflammatory response.[25,26] Inflammatory stimuli from cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL) -1a, IL-6, IL-17, and IL-18, as well as epidermal growth factors (EGF) that mediate inflammatory responses activated through interactions with Toll-like receptors (TLRs), IL-1 receptors (IL-1R), IL-6 receptors (IL-6R), and TNF receptors (TNR).[26,27]

In **Figure 2**, multiple mechanism of cancer-associated thrombosis is illustrated. Oncogenic MET, RAS, p53, or PTEN activation, besides promoting cancer, can also induced gene transcription involved in the hemostasis regulation such as PAI-1, COX-2, and TF. Tumor hypoxia also causes HIF-1α overexpression that directly controls the expression of hemostasis factors through the activation of PAI-1 and COX-2, or through MET.[25] The figure also shows that tumor-derived cytokines (IL-2, TNF and VEGF) can activate monocytes, platelets and endothelial cells. Tumor cells adhesion molecules (P-selectin, L-selectin) can bind the inflammatory cells which activate coagulation and stimulate fibrin production. Some predisposing factors can add to the overall prothrombotic phenotype in an individual cancer patients, such as obesity, diabetes, smoking habit, older age, hospitalization, surgery, central venous catheter (CVC) insertion, tumor compression stasis, ascites, and chemotherapy.[8,20,22]

Table 3. The risk factors for cancer-associated thrombosis.

Patient Characteristics	Cancer-Related Factors	Treatment-Related Factors	Biomarkers
Female sex	Site or origin of cancer	Hospitalization	High tissue factors expression
Older age	Tumor histology	Cancer therapy	Pre-chemotherapy platelet count > 350,000/uL
Race (African ethnicity)	Advanced stage and metastatic cancer	Erythropoiesis-stimulating agents	Pre-chemotherapy WBCs > 11,000/uL
Common comorbidities: diabetes, obesity, previous VTE, atherosclerosis, inflammation, others	Being in initial period after cancer diagnosis	Venous catheter	Elevated D-dimer
Inherited thrombophilia			High levels of: Plasma tissue factor Soluble P-selectin C-reactive protein von Willebrand factor Low expression of: ADAMTS13 gene

Abbreviations: VTE, venous thromboembolism; WBC, white blood cells; ADAMTS13,
Source: Eichinger S. *Thromb Res* 2016

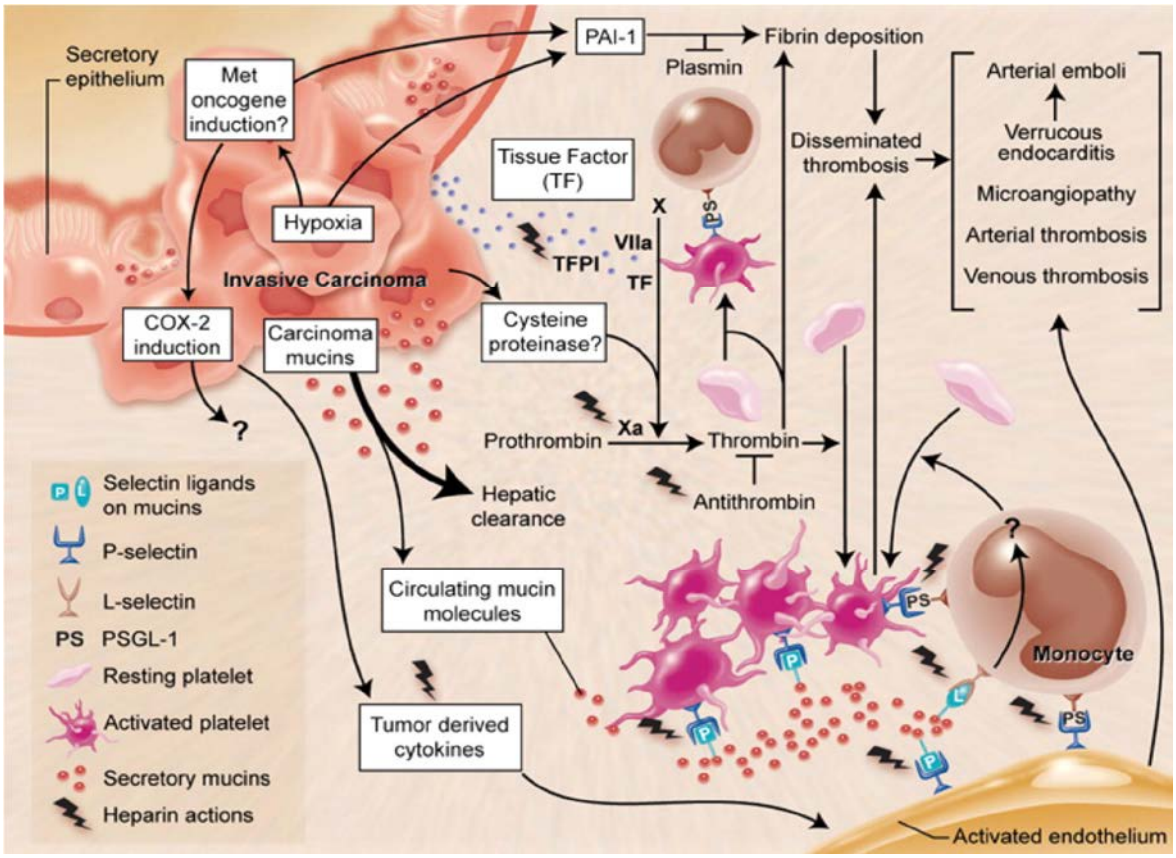

Figure 2. Multiple mechanisms in the pathophysiology of cancer-associated thrombosis. There are overlapping and interacting mechanisms that can explain the increased incidence of thrombosis (both arterial and venous thrombosis) in cancer patients. Hypercoagulability is ultimately the result of intrinsic and extrinsic risk factors. Reproduced with permission from Varki A, *Blood* 2007.

The administration of chemotherapy can lead to an inflammatory condition,[25] which triggers NF-κB and MAPK signaling pathways to produce proinflammatory cytokines, including IL-6, TNF-α, IL-1, IL-8, and CRP.[26] Proinflammatory cytokines play a role in thrombus formation in cancer patients and those undergoing chemotherapy. Inflammatory markers such as hs-CRP is correlated with Wells score and D-dimer, which can be used to predict the incidence of DVT in cancer.[28] Chemotherapy-induced vascular endothelial cell activation (VECA) is demonstrated by increased binding of circulating endothelial cells and von Willebrand factors (vWF) in the plasma.[29] vWF triggers platelets adhesion, factor VIII binding and transport, as well as thrombus formation.[30] Our study revealed that pre-chemotherapy levels of vWF:Ag and ADAMTS-13 are independent risk factors for DVT incidence among cancer patients.[31]

VTE RISK STRATIFICATION

In order to assess VTE risk in cancer patients, various factors need to be considered. Some risk models have been developed and validated. The most known is the Khorana risk score which is stratified into low (score 0), intermediate (score 1-2) and high risk (score 3) based on several variables such as cancer site, platelet count, WBCs count, hemoglobin levels or use of ESA, and BMI, as shown in **Table 4**. This model had a negative predictive value of 98.5%, positive predictive value of 7.1%, sensitivity of 40%, and specificity of 88%, as reported by a cohort study of 2,701 patients which was then validated into a prospective independent cohort study of 1,365 patients.[32] Some variations have been published such as PROTECH,[33] CONKO,[34] and Vienna CATS score,[35] which elaborate other biomarkers like D-dimer and soluble P-selectin.[36] The COMPASS-CAT[37] and ONKOTEV56[38] models were subsequently developed, which included

variables such as cardiovascular risk factors, history of VTE, presence of CVC, chemotherapy or hormonal therapy, tumor stage, and platelet count.

The risk of major bleeding must be considered when choosing pharmacological VTE prophylaxis in cancer patients for an optimal outcome. Regardless of the selection of anticoagulation, the primary contraindication to prophylactic anticoagulant are bleeding episodes.[39,40] The evidence-derived IMPROVE Bleeding Score used 13 clinical and laboratory factors and designated a score of seven or more to identify a patient cohort (10% of the population) at a high risk of bleeding (major bleed risk), 4.1% vs. 0.4%. Patients with a score of less than seven were considered at a lower risk of bleeding (**Table 5**).[41] Sex and age are the fixed risk factors, while the remaining are modifiable risk factors. When deciding whether anticoagulant can be safely initiated in a prophylaxis setting, clinicians should always optimize the patient's current clinical status.

Table 4. Predictive models for chemotherapy-related VTE in ambulatory cancer patients (Khorana risk score).

Patient Characteristics	VTE Risk Score
Cancer origin	
Very high risk	2
Primary brain, gastric, or pancreatic tumors	
High risk	1
Lung, lymphoma, gynecologic, or genitourinary tumors, excluding the prostate, and myeloma	
Low risk	0
Breast, colorectal, or head and neck tumors	
Other characteristics	
Platelet count ≥ 350x10^6/uL	1
WBCs count > 11 x 10^3/uL	1
Hemoglobin <10 g/dL or use of red blood cell growth factors	1
BMI ≥ 35 kg/m^2	1
NOTES: Low risk: 0 score; intermediate risk 1 or 2 score; high risk: 3 or higher score	

Abbreviations: BMI: body mass index; WBC, white blood cells
Source: Khorana AA, et al. Blood 2008.

Table 5. IMPROVE bleeding risk score.

Variables			Bleeding Risk Score
Fixed (non-modifiable) risk factors	Age	≥ 85 years	3.5
		40 to 84 years	1.5
		< 40 years	0
	Gender	Male	1
		Female	0
Modifiable risk factors	Kidney function	Severe kidney impairment (GFR ≤ 30 mL/min/m^2)	2.5
		Moderate kidney impairment (GFR 30 to 59 mL/min/m^2)	1
		Normal kidney function (GFR ≥ 60 mL/min/m^2)	0
	Liver function	Liver failure (INR ≥ 1.5)	2.5
		Normal liver function (INR <1.5)	0
	Platelets	<50 x 10^6/uL	4
		≥50 x 10^6/uL	0
	Other factors	Active gastric or duodenal ulcers	4.5
		Prior bleeding within last 3 months	4
		Admission to ICU or CCU	2.5
		Central venous catheter	2
		Active malignancy	2
		Rheumatic disease	2
NOTES: Low risk: score <7; increased risk: score ≥7			

Abbreviations: INR: international normalized ratio, GFR: glomerular filtration rate, ICU: intensive care unit, CCU: coronary care unit
Source: Skeik N, Westegard E. *Ann Vasc Dis* 2020.

CURRENT EVIDENCE

The VTE prophylaxis guideline in cancer patients with anticoagulants such as unfractionated heparin (UFH), low molecular weight heparin (LMWH), direct oral anticoagulant (DOAC) including rivaroxaban or apixaban has been recommended by the American Society of Clinical Oncology (ASCO),[42] International Initiative on Thrombosis and Cancer (ITAC),[43] National Comprehensive Cancer Network (NCCN)[44] and also the national guideline from *Perhimpunan Trombosis Hemostasis Indonesia* (PTHI) or the Indonesian Society on Thrombosis Hemostasis (InaSTH).[12]

The results of recent clinical trials support the benefits and safety of VTE prophylaxis in medical patients. These clinical trials have compared enoxaparin, dalteparin, and fondaparinux to placebo in patients with acute medical illnesses. The use of enoxaparin in the Medical Patients with Enoxaparin (MEDENOX) trial,[45] dalteparin in the Prevention of VTE in Immobilized Patients (PREVENT) trial,[46] fondaparinux in the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTeMIS) trial,[47] and rivaroxaban in the CASSINI trial[48] were each compared to placebo. All studies show a significant decrease in the incidence of VTE. These results support the evidence-based recommendations for the use of thromboprophylaxis in clinical practice.

PRIMARY THROMBOPROPHYLAXIS: CHOICE, DOSE AND DURATION

Routine thromboprophylaxis is not recommended in all patients with cancer, particularly ambulatory patients. Thrombo-prophylaxis should be offered to patients with a high risk of thrombosis, including patients with myeloma receiving thalidomide or lenalidomide, and specific strategies for patients with myeloproliferative diseases should be determined.

We proposed a Khorana score-based decision algorithm for thromboprophylaxis administration to cancer patients. An aggregate score of zero indicates low risk (0.8% risk of VTE over the course of 4 chemotherapy cycles), score 1-2 indicates intermediate risk (1.8%) and score 3 or greater indicates high risk (7.1%). Cumulative VTE risk have been estimated at 17.7% in the high risk group.[39] More recent publications have suggested that high risk may be reflected by a score of 2 or greater when accommodating both inpatient and outpatient cancer populations.[49,50] The second mentioned was based on Khorana risk score ≥2 associated with the presence of metastasis, vascular compression, and previous VTE.

Thromboprophylaxis may be recommended in patients with a Khorana score of <2 whether there were addition of other risk factors such as prior VTE, known thrombophilia, or BMI >40 kg/m^2. Caution should be in mind for patients with high bleeding risk, unresected tumors, impaired or fluctuating renal function, highly emetogenic chemotherapy agents limiting reliable oral intake, and drug-to-drug interactions. The proposed thromboprophylaxis chart is illustrated in **Figure 4**.

Prophylaxis for medical patients:[42]

1. Pharmacologic thromboprophylaxis is recommended for hospitalized patients with acute medical illness and reduced mobility, in the absence of bleeding and other contraindications.
2. Routine pharmacologic thromboprophylaxis is not recommended in patients admitted for minor procedures or chemotherapy infusion, or in patients undergoing bone marrow transplantation.

Prophylaxis for cancer patients undergoing systemic chemotherapy:[42,43]

1. Routine pharmacologic thromboprophylaxis is not recommended for all cancer outpatients.
2. High-risk cancer outpatients (Khorana score of 2 or higher), can be recommended to receive thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) prior to starting a new chemotherapy regimen, provided that there are no significant risk factors for bleeding and in the absence of drug interactions. Considerations for such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug costs, and duration of prophylaxis.
3. Patients with multiple myeloma receiving thalidomide or lenalidomide-based regimens

with chemotherapy and/or dexamethasone are recommended to receive pharmacologic thromboprophylaxis with either aspirin or LMWH for low-risk patients and LMWH for high-risk patients.

Prophylaxis for cancer patients undergoing surgery:[42]

1. All cancer patients undergoing major surgery is recommended to receive pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) or LMWH unless contraindicated due to active bleeding, high bleeding risk, or other contraindications.
2. Mechanical prophylaxis may be added to pharmacologic thromboprophylaxis but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated due to active bleeding or high bleeding risk.
3. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in high-risk patients.
4. Pharmacologic thromboprophylaxis for cancer patients undergoing major surgery should be continued for at least 7 to 10 days. Extended prophylaxis with LMWH for up to 4 weeks post-operatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for high-risk patients, such as those with restricted mobility, obesity, history of VTE, or with other risk factors.

The algorithm for thromboprophylaxis need to be individualized and the expected benefits should always outweigh the risk of bleeding. As depicted in **Figure 3,** major surgery and hospitalization are important risk factors for VTE in cancer patients. If the bleeding risk is fair or low, then primary thromboprophylaxis can be recommended.

Information about anticoagulant dosing for thromboprophylaxis in cancer patients are provided based information on **Table 7**.

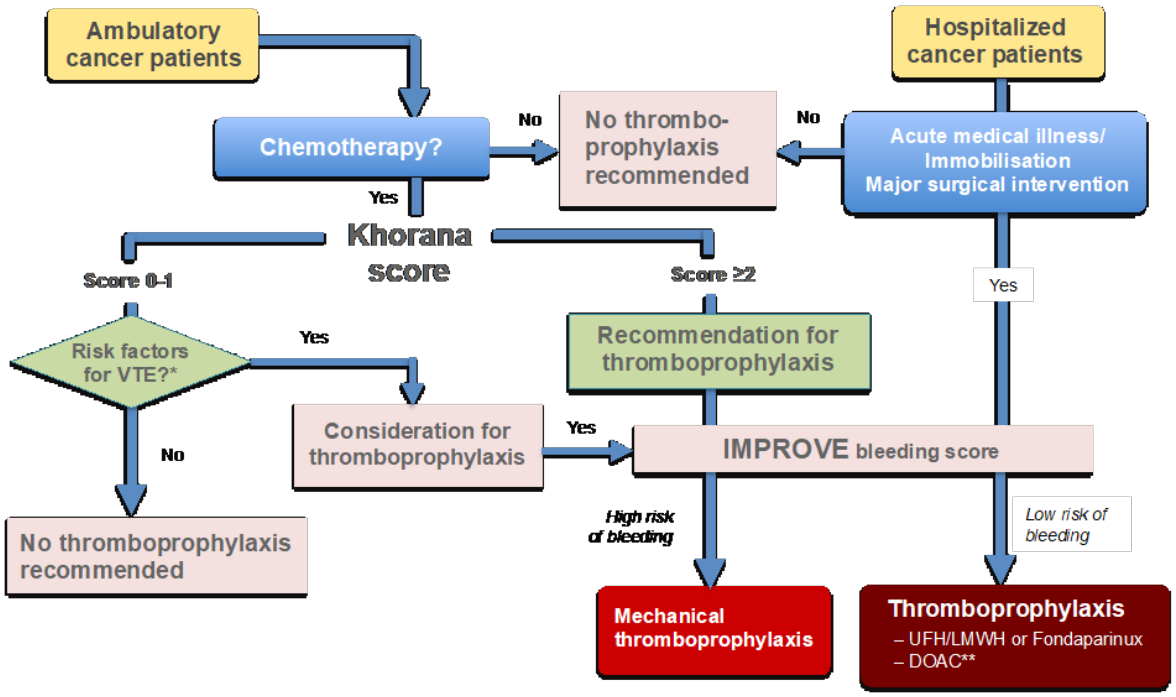

Figure 3. Daily practice algorithm for individual decisions for thromboprophylaxis in cancer patients.
Abbrebiations: LMWH, low moeluclar weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism
*Additional risk factors for thrombosis include: prior VTE, known thrombophilia, or BMI >40 kg/m^2 (see text for detail).
** DOAC can be considered only in non-gastrointestinal cancers

Table 7. Anticoagulant dosing regimens for prophylaxis in cancer patients.

Clinical background	Agent	Dose
Hospitalized cancer patients for medical reason(s)	UFH	5000 U every 8 hours sq
	Dalteparin	5000 U every 24 hours sq
	Enoxaparin	40 mg every 24 hours sq
	Fondaparinux	2.5 mg every 24 hours sq
Cancer patients undergoing surgery	UFH	5000 U 2-4 hours sq preoperatively and then every 8 hours thereafter
	Dalteparin	2500 U 2-4 hours sq preoperatively and 5000 U every 24 hours thereafter or 5000 U 2-4 sq hours preoperatively or 10-12 hours preoperatively and 5000 U every 24 hours thereafter
	Enoxaparin	40 mg 2-4 hours sq preoperatively or 10-12 hours preoperatively and 40 mg/24 hours thereafter
	Fondaparinux	2.5 mg every 24 hours sq beginning 6-8 hours postoperatively
Outpatient setting	Dalteparin	5000 U every 24 hours sq
	Enoxaparin	40 mg every 24 hours sq
	Fondaparinux	2.5 mg every 24 hours sq
	Apixaban	2.5 mg orally every 12 hours po
	Rivaroxaban	10 mg orally every 24 hours po

Abbreviations: p.o., per oral; sq, subcutaneously; UFH, unfractionated heparin
Source: Key NS et al. J Clin Oncol 2019.

SECONDARY PROPHYLAXIS

The concept of anticoagulant therapy (with proven existing VTE) can involve prolonged therapy for more than 3-6 months by noting that active cancer is a risk factor for VTE, with an annual recurrence rate of 10 to 29%. Considerations include: cancer type and activity, burden of disease, therapy, patient preference, immobilization, and life expectancy.[51] The NCCN guidelines recommends LMWH as the preferred treatment for the first 6 months, or DOAC (rivaroxaban) if the patient refuses to be injected or is not a candidate for subcutanoues medication for several reasons.[52]

THE NEW PARADIGM OF CANCER-RELATED THROMBOPROPHYLAXIS

Despite the existence of published guidelines and studies regarding the benefits and safety of VTE prophylaxis, we continue to see low adoption of such recommendations, and VTE prophylaxis remains underused.[53,56] The reason behind the low provision of prophylaxis in patients with high risk of VTE is most often due to cost considerations,[53,55,57] concerns of bleeding complications,[54,56] lack of knowledge and confidence,[54] lack of awareness,[55,58] and reluctance to give daily injections of anticoagulants as prophylaxis.[54]

Recent advances in understanding the mechanism of VTE demonstrate the pivotal role of the immune system and inflammation in its pathogenesis, and show that it is an immunity and inflammation-related process rather than merely coagulation-dependent thrombosis. The above paradigm opens new ideas for further research on new therapeutic options for VTE prophylaxis by inhibiting immune and inflammatory processes, instead of inhibiting the coagulation factors on the coagulation cascade directly, thereby reducing the risk of bleeding that can occur with the administration of anticoagulants as VTE prophylaxis.[59] Currently, there is no specific guideline for arterial thrombosis in cancer patients due to the lack of specific data available. However, usual care is recommended.

CONCLUSION

Thromboembolism events remain highly prevalent in cancer patients. Venous

thromboembolism is a leading cause of death, morbidity, delayed treatment, and increased treatment cost. The high morbidity and mortality of VTE raises the need for thromboprophylaxis to reduce the incidence of these clinical conditions. The administration of effective VTE prophylaxis and treatment in cancer patients can improve their survival rate and quality of life. Today, there are several options in medical thromboprophylaxis that include UFH, LMWH, and more recently DOAC also have been validated in several clinical trials involving patients with cancer. The decision to choose one anticoagulant over another was based on clinical ground, type of cancer, risk of bleeding, renal function, patient compliance, social economic religion aspects and finally, patient's preferences.

Recent advances in understanding the mechanism of VTE demonstrate the pivotal role of the immune system and inflammation in its pathogenesis, and show that VTE is an inflammation-related process, instead of merely coagulation-dependent thrombosis. The above paradigm opens new insights for further research on new therapeutic options for VTE prophylaxis by inhibiting immune and inflammatory processes, instead of inhibiting the coagulation factors on the coagulation cascade directly, thereby reducing the risk of bleeding that can occur with the administration of anticoagulants as VTE prophylaxis.

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