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Review Article

Management of cancer-associated venous thromboembolism (CAT): Expert opinion and insights from the current guidelines

Nuri Karadurmus[1], Suat Doganci[2], Mehmet Ali Nahit Sendur[3], Onur Saydam[4], Begum Ozdengulsun[4], Emine Ahi Dundar[4], Hakki Tankut Akay[5]

[1]University of Health Sciences, Gülhane Training and Research Hospital, Department of Medical Oncology, Ankara, Türkiye
[2]University of Health Sciences, Gülhane Training and Research Hospital, Department of Cardiovascular Surgery, Ankara, Türkiye
[3]Ankara Bilkent City Hospital, Department of Medical Oncology, Ankara, Türkiye
[4]Pfizer Türkiye, Department of Primary Care-IM-Cardiovascular, İstanbul, Türkiye
[5]Başkent University Ankara Hospital, Department of Cardiovascular Surgery, Ankara, Türkiye

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Abstract

Venous thromboembolism (VTE) poses a significant concern for cancer patients, contributing to increased morbidity and mortality rates. This review explores the epidemiology, risk factors, and therapeutic strategies pertinent to cancer-associated thrombosis (CAT). It underscores the critical role of risk assessment models, the efficacy of anticoagulant therapies, and the necessity for personalized treatment approaches to optimally manage CAT. Additionally, the review examines the specific characteristics of CAT patients in Türkiye, emphasizing the importance of vigilant monitoring and management to reduce VTE risks in oncology patients. The insights presented aim to refine clinical practices and enhance patient outcomes by addressing existing gaps and proposing effective solutions for improved CAT management.

Keywords: Venous thromboembolism, neoplasms, anticoagulants, direct-acting oral anticoagulants, low molecular weight heparin

INTRODUCTION

Venous thromboembolism (VTE) affects 1 in 12 people in their lifetime and the increase in disease burden is often linked with lifestyle changes, rising obesity, and chronic health issues [1]. Similarly, advancing age, lifestyle, risk factors, industrialization, and better screening have also led to increased cancer cases.

The significant link between cancer and thrombotic events has been known since 1865, when Armand Trousseau first reported it [2]. The rate of cancer-associated thrombosis (CAT) has risen significantly over the last 20 years [3,4]. For instance, the 12-month rate of VTE among cancer patients increased from 1% in 1997 to 3.4% in 2017, while the VTE risk in non-cancer individuals remained stable [4,5]. This increase can be attributed to the improved overall survival of cancer patients, the increased use of chemotherapy, the development of novel therapies, and the implementation of better diagnostic methods [4,5]. Recent data indicates that VTE is developed in approximately 4-20% of cancer cases and is the second leading cause of cancer-related deaths [6]. Cancer patients are 4-8 times more likely to develop VTE than those without cancer [6]. Around 20-30% of all first VTE events are cancer-associated [7]. These statistics underscore

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Corresponding Author: Onur Saydam, Pfizer Türkiye, Department of Primary Care-IM-Cardiovascular, İstanbul, Türkiye
Email: onur.saydam@pfizer.com

the serious public health problem posed by CAT, highlighting the need for vigilant management and awareness of VTE risk in cancer patients and the possibility of underlying cancer in VTE patients.

Although VTE is the most common thrombosis in cancer patients, it can also appear as catheter-associated thrombosis, disseminated intravascular coagulation, and arterial thrombosis due to the hypercoagulable state caused by malignancy and treatments [8]. These events significantly affect morbidity and mortality, requiring vigilant monitoring and management [9]. This review aims to identify unmet needs and propose solutions for better clinical practice and improved management of CAT.

1. CAT in Türkiye

The characteristics of CAT patients in Türkiye were examined in a retrospective study (CAT-TR) [10]. Among 35,131 patients with deep vein thrombosis (DVT) in proximal lower extremities in 17 centers, the prevalence of VTE was determined as 8.3% (n= 2936). National CAT-TR data, which consistently reflected the daily clinical practice of Turkish medical oncologists, revealed that 70.3% of oncology patients had advanced cancer, and they received chemotherapy or targeted therapy. Lung cancer was the leading cancer type, which was associated with VTE (30%), followed by colon (8.6%), breast (6.8%), gastric (5.5%), and pancreas (3.8%) cancers [10]. The results of CAT-TR are consistent with the GLOBOCAN 2020 registry data, which have reported that lung cancer is the most prevalent in Türkiye, with 41,000 new cases in 2020 [11].

The current literature indicates that breast, prostate, colorectal, and lung cancers primarily contribute to the overall prevalence of CAT [3,12]. However, lung cancer ranks as the highest cancer type complicated by CAT development in Türkiye as it is the most prevalent in the population [12].

In patients with pancreatic cancer, especially with masses located in the corpus/cauda, there is a 2-3-fold increased risk of VTE compared to the tumors of the pancreas head [13]. However, in patients with pancreatic cancer, targeted and immuno- therapies are still under development. Therefore, the survival period in patients with pancreatic cancer is approximately 8-10 months. The short survival durations of patients diagnosed with pancreatic cancer may reduce the possibility of CAT development during the disease. One of the factors contributing to the high incidence of lung cancer in Türkiye is that, despite a decline in smoking rates over the years, they remain above the global average [14,15]. Consequently, CAT data for oncology patients in Türkiye often come from those with lung cancer.

2. Risk Factors in the Development of CAT

There are several risk factors leading to the development of CAT (Figure 1) [16]. The risk factors for VTE in non-cancer populations such as advanced age, immobility, history of thrombosis, and obesity, are also relevant to the development of CAT. Additional risk factors in oncology patients can be classified depending on the characteristics of tumor masses, patients (i.e., immobilization, comorbidities), and treatment-related factors (Table 1) [16,17]. Although these factors theoretically predispose 5-10% to the development of CAT, the 5- to 10-year cumulative incidence ranges from 25% to 30% [7,18].

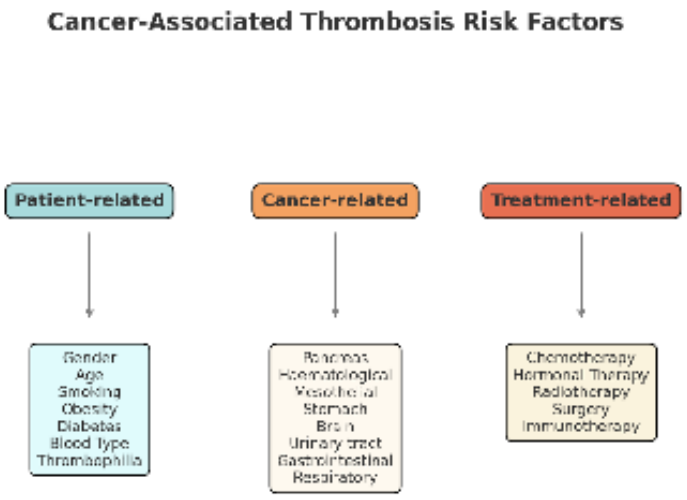

Figure 1. Common risk factors for cancer, arterial thromboembolism, and venous thromboembolism [16]

Table 1. Risk factors for cancer-associated thrombosis [17]

Cancer type	Increased risk of pancreatic, brain, lung, and ovarian cancer
Cancer stage	Increased risk with metastatic spread
Cancer-directed therapy	Increased risk with myeloma therapy (thalidomide, lenalidomide), antiangiogenic agents (bevacizumab), and antiestrogen therapy

2a. Cellular tumor-related factors

The tumor's procoagulant activity, which induces prothrombin, substances such as prostacyclin, endothelium-dependent relaxing factor, or thrombomodulin released from the endothelium, particles detached from the tumor mass, and the formation of a hypercoagulable state because of the vascular sources of the tumor mass can lead to the development of CAT [3].

Tissue factor, a transmembrane glycoprotein, is considered to be the most critical factor in procoagulant activity in cancer

patients [6]. In combination with factor (F) VII, it acts as a cofactor in extrinsic pathway-mediated coagulation and helps activate coagulation. Microparticles carrying tissue factor and detaching from the tumor mass were found to be elevated in 60% of cancer patients with VTE, compared to 27% in those without VTE. Additionally, certain oncogenes and tumor suppressor gene molecules that appear during the oncogenesis process can increase tissue factor expression and alter the phenotypic characteristics of the tumor cell [19]. These include activation of the MET oncogene, inactivation of the PTEN tumor suppressor gene, and K-ras and p53 mutations [20].

Other molecules that play a role in hemostasis changes in the oncological disease process include cancer procoagulant, proinflammatory cytokines (tumor necrosis factor-alpha, interleukin 1 beta), pro-angiogenic factors (vascular endothelial growth factor and basic fibroblast growth factor) and fibroblast growth factors [21]. In particular, gastrointestinal (GI) tumors stimulate coagulation by producing mucin, while tumor cell-host cell interaction increases receptors, activators, and inhibitors in the fibrinolytic system [13]. The heparanase enzyme contained in tumor cells breaks down heparan sulfate in the extracellular matrix, facilitates tumor cell spread and metastasis, and increases tissue factor expression on the cell surface. Neutrophil extracellular trap formation activates coagulation and contributes to hypercoagulability, inflammation, tumor growth, tumor spread, and new vessel formation [6]. For example, while non-Hodgkin lymphoma and Hodgkin disease are less thrombogenic, some cancers, such as adenocarcinomas of the abdominal organs (pancreas, gastric), small cell lung cancer, primary tumors of the brain, and blood cancers, are more thrombogenic [3].

2b. Anatomical tumor-related factors

External or direct invasion of large vessels by the tumor is a risk factor. The most typical example is renal cell carcinoma, in which the prevalence of tumor thrombosis invasion is reported at 10% to 18% in the renal vein and 4% to 23% in the inferior vena cava [22]. Factors such as hepatocellular carcinoma compressing the hepatic vein, lymphomas compressing conglomerate lymph nodes, mediastinal tumors, and thymomas can be given as examples. The thrombotic risk in pancreas tumors depends on their anatomical location. While the risk is 70% in masses located in the body or tail of the pancreas, it is lower when located in the head. The variability of ratios indicates that the development of CAT also depends on the anatomical location of the mass in the organ and tumor histopathology [23,24].

2c. Factors related to patient characteristics

General risk factors such as age, female gender, obesity (body mass index >35 kg/m^2), presence of concomitant diseases, bed rest, and past and family history of VTE are also valid for cancer patients [6]. It is reported that non-O blood type is a time-dependent predictor of VTE in patients with cancer, and it is associated with increased VTE risk beyond 3 months of follow-up and in patients with intermediate- and low-risk tumor types [25].

2d. Factors related to oncological therapy

Chemotherapy, radiotherapy, surgical interventions/ and central venous catheters are important thrombosis-inducing factors [26]. Chemotherapy is a significant risk factor for VTE occurrence. It is a frequent cause of hospital admission and is associated with a 6-fold increase in VTE risk [27]. Moreover, chemotherapy increases the VTE risk in patients ≥70 years of age by 2-fold when compared to younger patients [28]. The use of Bevacizumab and cisplatin in combination with taxanes can increase hypercoagulability [26].

New treatment agents currently used in oncology practice may also increase the risk of thrombosis. Among these new agents, CDK4/6 inhibitors, a class of medicines indicated for certain types of hormone receptor-positive breast cancer, are increasingly used in daily oncological practice. Thrombosis risks may vary from 5% with abemaciclib [29] and 37% in the first 3 months of treatment with amivantamab [30]. Bevacizumab is another commonly used immunotherapy associated with higher arterial (particularly cardiac and cerebral ischemia) and venous adverse events among oncology patients [31].

As novel anticancer agents have become an indispensable part of the therapeutic arsenal for various cancer types, physicians must be more aware of CAT prophylaxis when using them in daily oncology practice. As outlined in the current international guidelines, increased awareness among physicians would lead to risk stratification during oncological patient follow-up.

3. Risk Assessment for CAT Patients

The most rational approach to prevent the development of CAT is identifying high-risk oncology patients at diagnosis and initiating anticoagulation. Khorana et al. developed a model combining clinical factors and laboratory markers for ambulatory cancer patients receiving chemotherapy [32]. In the Vienna CAT study, two more biomarkers (P-selectin and D-dimer) were added, and the predictive value for CAT increased significantly [6,33]. The COMPASS-CAT score is a validated model that predicts VTE in ambulatory patients with breast, colon, lung, and ovarian cancers receiving therapy in the US. It helps identify high-risk individuals who may benefit from primary thromboprophylaxis [34].

Since the development of thrombotic events is a dynamic process, performing a risk assessment once is insufficient. The ASCO panel and the ESMO 2023 Clinical Guideline recommend that risk assessment models be repeated periodically throughout the disease to assess the risk of thrombosis in cancer patients (Table 2) [3,6,35].

Table 2. Khorana and V-CATS VTE risk assessment models [6]

Risk factor		Points
Cancer location	Very high-risk cancer (gastric, pancreas)	2
	High-risk cancer (lung, lymphoma, gynecologic, bladder, testicular)	1
Thrombocyte count ≥350000 /mm^3		1
Leukocyte count ≥110000 /mm^3		1
Hemoglobin <10 g/dL and/or using erythropoiesis-stimulating drugs		1
Body mass index ≥35 kg/m^2		1
Biomarkers added after the Vienna Cancer and Thrombosis Study (CATS)		
D-dimer ≥1.44 mcg/mL		1
P-selectin ≥1.53 mg/mL		1

*Total score=0 implies low risk (VTE risk: 0.8-3%); 1-2=moderate risk (VTE risk: 1.8-8.4%); ≥3=high risk (VTE risk: 7.1-41%)

4. Evaluation of VTE Recurrence Risk in Patients with CAT

It is crucial to monitor patients with CAT closely to determine the high-risk populations for recurrence and long-term anticoagulation.

The Ottawa score has been developed to predict VTE recurrence in cancer patients. Its effectiveness in distinguishing between low and high risks of VTE recurrence has been well documented (Table 3) [36].

Table 3. Ottawa score: prediction of VTE recurrence in cancer patients [36]

Variable	Regression coefficient	Points
Female gender	0.59	1
Lung cancer	0.94	1
Breast cancer	-0.76	-1
TNM* Stage I	-1.74	-2
Previous VTE	0.40	1
Clinical probability		Points
Low risk (≤0)		-3 to 0
High risk (≥1)		1 to 3

VTE indicates venous thromboembolism [Edited]; *TNM (tumor-nodes-metastasis staging system) for solid tumors only

Since D-dimer values can be misleading in cancer patients, they are not recommended to be used for the decision-making regarding extended treatment or to elongate anticoagulation according to risk factors [6,37,38]. For assessing recurrence risk in cancer patients, it is advised to check if the malignancy is active or in remission. The decision to extend the treatment should be made according to the presence of active disease and receiving active cancer treatments. Some experts prefer to continue anticoagulant treatments at therapeutic doses in these patients and report that, according to their clinical experience, long-term use of anticoagulants at therapeutic doses is safe [39]. However, recent evidence indicates that low-dose anticoagulation can be an effective and safe option for CAT patients in secondary prophylaxis [40].

Despite adequate anticoagulation, the risk of recurrence for patients with active cancers is high and variable [41]. A key factor contributing to the high risk of recurrence in active cancer patients is the frequent discontinuation or interruption of anticoagulants, as well as extended gaps between treatments.

Furthermore, in cancer patients, decreased drug absorption, procedures, interruption of anticoagulant treatment because of bleeding, changing dose requirements in anticoagulation, and drug-drug interactions are also essential reasons that disrupt the therapeutic range [41]. Treatment adherence and persistence may also lead to the interruption of anticoagulation treatment and may affect the risk of recurrence. Patients with certain types of cancer, those receiving hormonal treatment, those with comorbidities, those using central venous catheters, those presenting with pulmonary embolism (PE) at initial diagnosis, patients in the first 3 months of cancer, and patients with high VTE risk, such as pancreatic and gastric cancers, may be at an increased risk of VTE, as well as cancer recurrence [41,42].

5. Primary Pharmacological Thromboprophylaxis in CAT

Current international and local guidelines primarily focus on VTE treatment; however, prophylaxis remains in the gray area. The choice of thromboprophylaxis approach should depend on the patient's diet, ability to take oral medication, the stage of the tumor, the patient's bleeding risk level, the location of the cancer,

drug availability, and cost, whether the patient is receiving the treatment in ambulatory settings or hospitalized [3,6,35].

5a. Primary pharmacological thromboprophylaxis in patients with cancer hospitalized for an acute medical illness

Pharmacologic thromboprophylaxis is recommended for hospitalized patients with active malignancy unless there is active bleeding or other contraindications. However, it should not be indicated for patients admitted only for minor procedures, chemotherapy infusion, or patients undergoing stem-cell/bone marrow transplantation [35].

Studies have shown that low molecular weight heparin (LMWH), unfractionated heparin (UH), and fondaparinux are effective in VTE prophylaxis among hospitalized patients, including cancer patients [6]. In daily clinical practice, LMWH is generally preferred to UH, due to its ease of administration.

Unless contraindicated for anticoagulation, all cancer patients with active disease who are hospitalized, receive heparin (mostly LMWH) as prophylaxis in Türkiye. Besides, optimal risk assessment should be performed when patients are discharged.

5b. VTE prophylaxis for ambulatory patients with cancer during systemic chemotherapy

The routine use of pharmacological agents to prevent thromboembolism is not recommended for oncology patients in the ambulatory setting. Guidelines recommend considering primary thromboprophylaxis when the estimated risk of VTE>8%-10% (i.e., patients with a Khorana score≥2) in the absence of major bleeding risk factors and drug interactions [35]. ASCO guideline suggests that thromboprophylaxis with apixaban, rivaroxaban, or LMWH may be considered for ambulatory cancer patients at high risk for primary prophylaxis for a maximum of 6 months [35].

However, in Türkiye, primary prophylaxis is not sufficiently widespread in daily clinical practice. Due to the oncologists' daily workload, ambulatory cancer patients are inadequately assessed for VTE risks. There are also labelling and reimbursement restrictions for a direct oral anticoagulant (DOAC) to be used for prophylaxis in Türkiye for ambulatory cancer patients. Table 4 presents the label information of three commonly employed DOACs [43-45].

Table 4. The Turkish label information of DOACs for cancer patients diagnosed with VTE [43-45]

Apixaban	Patients with active cancer may be at high risk for both VTE and bleeding events. Apixaban, when considered for use in the treatment of DVT or PE in cancer patients, the benefits should be carefully weighed against the risks [43]
Edoxaban	The efficacy and safety of edoxaban in the treatment and/or prevention of VTE in patients with active cancer have not been established yet [44]
Rivaroxaban	Patients with malignancy may also face a high risk of bleeding and thrombosis. The individual benefit of antithrombotic therapy should be assessed against the risk of bleeding in patients with active cancer, depending on the location of the tumor, the antineoplastic therapy, and the stage of the disease. Tumors located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy. Rivaroxaban use is contraindicated in patients with malignant neoplasm with a high risk of bleeding [45]

5c. Patients with cancer undergoing surgery receive perioperative VTE prophylaxis

For cancer patients undergoing major surgery, pharmacologic thromboprophylaxis with UH or LMWH is recommended unless there is active or high-risk bleeding. Prophylaxis should start preoperatively and last 7-10 days. It should be continued for 28 days, which is advised for patients with high-risk features after major abdominal or pelvic surgery. This duration can be extended for orthopedic surgery for up to 3 months. According to international guidelines, apixaban or rivaroxaban can be an alternative to LMWH for extended prophylaxis [3,35]. However, there are also labelling and reimbursement restrictions for DOACs to be used for prophylaxis in Türkiye for cancer patients undergoing surgery. Mechanical methods such as stocking socks are adjunctive to pharmacologic methods and should not be used alone unless pharmacologic methods are contraindicated [3].

5d. Prophylaxis of catheter-related thrombosis

Anticoagulation is not recommended as a regular preventive measure for thrombosis related to catheters. However, the type and location of the catheter may also affect the risk of thrombosis. A study revealed that peripherally inserted central catheters had a much higher risk of VTE and adverse events than implanted port catheters. On the other hand, arm ports had a higher VTE risk than chest ports [46]. Choosing the best alternative for the patient may reduce the risk of catheter-related thrombosis [47].

6. Treatment and Secondary Prophylaxis/Long-term and Extended Anticoagulation in CAT

Optimal management of CAT is crucial for clinical outcomes. Inappropriate treatment entails both a risk of VTE recurrence and a risk of major bleeding in the initial phase after the thromboembolic event. However, the VTE recurrence risk and its case fatality rate are higher than those of major bleeding, so anticoagulant treatment should be given to all CAT patients for at least three to six months unless there are contraindications [48]. The optimal anticoagulant treatment for these patients is a matter of debate. Another issue is the residual risk of VTE recurrence after six months of the initial CAT event. This risk should be appropriately assessed to identify the patients who would benefit from continued anticoagulant treatment and the type of treatment to be used [35,49].

6a. Initial phase

When selecting initial treatment options, it is essential to consider patient-specific factors such as weight, renal function, anemia, and thrombocytopenia. Initial anticoagulation may involve LMWH, UH, fondaparinux, apixaban or rivaroxaban. For patients starting parenteral anticoagulation, LMWH is preferred over UH during the initial anticoagulation phase for cancer patients with newly diagnosed VTE without severe renal impairment (defined as creatinine clearance, 15-30 mL/min) [38]. When LMWH or DOACs are not available or contraindicated, unfractionated heparin can be an alternative for the initial management of established VTE in cancer patients. Fondaparinux can also be an option for the initial management of established VTE in cancer patients [50].

Thrombolysis can be considered for cancer patients with established VTE only on an individual basis with careful evaluation of contraindications [50]. The risk of bleeding, such as cerebral metastasis, should be eliminated. The procedure should be performed in centers with health-care practitioners with the appropriate expertise.

In the initial management of VTE, inferior vena cava filters may be indicated when anticoagulation is contraindicated or, in the case of pulmonary embolism, when recurrence occurs despite optimal anticoagulation. Contraindications for anticoagulation should be reassessed periodically, and anticoagulation should be restarted when feasible [50].

6b. Treatment phase (up to 6 months)

DOACs are suggested for cancer patients whose creatinine clearance is>30 ml/min unless there are significant drug-drug interactions or impaired gastrointestinal absorption. The management of CAT has been extensively evaluated in major randomized clinical trials such as SELECT-D, CARAVAGGIO, and Hokusai-VTE Cancer, focusing on the efficacy and safety of DOACs. The SELECT-D trial showed that rivaroxaban reduced the recurrence of VTE compared to dalteparin, although there was a three-fold relative increase in CRNMB with rivaroxaban. According to SELECT-D, rivaroxaban should be used with particular caution in patients with esophageal cancer [51]. In the CARAVAGGIO study, apixaban showed comparable efficacy to dalteparin, with no significant difference in major bleeding events, including major gastrointestinal bleeding [52]. The Hokusai-VTE Cancer trial showed that recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban compared to dalteparin. This difference resulted from an increased rate of upper gastrointestinal bleeding with edoxaban [53]. The efficacy and safety results of apixaban, rivaroxaban and edoxaban compared to deltaparin are summarized in Table 5. These findings indicate that DOACs can be an effective alternative for certain patients, highlighting the need for individualized treatment strategies that consider bleeding risks. Caution is advised in patients with gastrointestinal malignancies, especially in the upper gastrointestinal tract. The Garfield-VTE study found that patients with active cancer had higher rates of major bleeding, with gynecological (15.7%), upper gastrointestinal (14.3%), and colorectal cancers (11.4%) being the most common types [54]. The available evidence indicates an increased risk of gastrointestinal bleeding with edoxaban and rivaroxaban [50]. If a DOAC is preferred in these patient groups, apixaban may be chosen. LMWHs are favored over vitamin K antagonists for VTE management, but daily subcutaneous injections for long durations may be challenging for patients. For patients with cancer and confirmed VTE, anticoagulation with LMWH or direct oral anticoagulants should be continued for at least 6 months. The 2021 American Society of Hematology and 2021 Second Update of the CHEST guidelines suggest the usage of DOAC over LMWH for up to 6 months of treatment for patients with active cancer [55,56]. Beyond 6 months, the decision to stop or maintain anticoagulation (LMWH, direct oral anticoagulants, or vitamin K antagonists) should depend on the individual assessment of the benefit-risk ratio, tolerability, drug availability, patient preference, and cancer activity [50].

Table 5. Efficacy and safety results of DOACs vs. LMWHs [51-53]

	Apixaban vs. Deltaparin				Edoxaban (after 5 days low-molecular weight heparin) vs. Deltaparin				Rivaroxaban vs. Deltaparin			
	Risk	HR	95% CI	P value	Risk	HR	95% CI	P value	Risk	HR	95% CI	P value
VTE recurrence	↔	0.63	0.37-1.07	0.09	↔	0.71	0.48-1.06	0.09	↓	0.43	0.19-0.99	--
Major bleeding	↔	0.82	0.40-1.69	0.60	↑	1.77	1.03-3.04	0.04	↔	1.83	0.68-4.96	--
Major GI bleeding	↔	1.05	0.44-2.50	--	*	--	--	--	*	--	--	--
All-cause mortality	↔	0.82	0.62-1.09	--	↔	1.14	0.90-1.45	--	--	--	--	--

*Most major bleeding events were due to gastrointestinal bleeding; According to the national guidelines on CAT, DOACs (apixaban, edoxaban, and rivaroxaban) are recommended as Class IA in the treatment of CAT; In patients with gastrointestinal system tumors, apixaban may be preferred as the first choice [57]

The 2021 Türkiye National Treatment Guideline for Peripheral Arterial and Vein Diseases recommends using LMWH and DOACs in cases of CAT (IA; very strong recommendation) [57]. This guideline emphasized that apixaban may be preferred in carefully selected patients with gastrointestinal tract tumors [57].

Panel members have mentioned that the CAT trials with DOACs didn't include patients with brain metastases, carcinoma of the skin and acute leukemia. They also have emphazied that vena cava filter insertion is commonly performed in daily clinical practice in Türkiye, it is not recommended to be performed in patients with established or chronic thrombosis (VTE diagnosis more than 4 weeks ago) or patients with temporary contraindications to anticoagulant therapy because of the absence of relevant evidence, unclear short-term benefit, and increasing evidence of long-term harm [35].

6c. Extended phase (>6 months)

The optimal duration of CAT treatment is unclear [3]. The current literature about extended anticoagulation for CAT suggests that the risk of thrombotic complications may remain significant beyond 6 months, so extension of anticoagulation may be considered in patients with active cancer receiving cancer treatment with an increased risk of recurrence. The RIETE registry revealed that less than half of cancer patients can complete extended anticoagulation due to bleeding risk or clinical deterioration, despite its benefits [58]. Therefore, periodic assessment of the risk-benefit profile and patient preferences remain crucial to evaluating the need for anticoagulation or dose adjustments. Studies have reported that the absence of residual vein thrombosis in patients with cancer and an index DVT indicates a low risk for recurrent thrombotic events.

For cancer patients at high risk for recurrent VTEs, long-term anticoagulation is preferred over short-term despite low evidence of net health benefit. This applies to those in palliative care not cured by or still undergoing anticancer treatment. The benefits usually outweigh the risks unless there is a major bleeding risk. Cancer patients should make informed decisions about long-term anticoagulation based on outcomes, benefit-harm assessment, and their preferences [41].

The optimal length of extended anticoagulation for secondary prevention of VTEs in patients with active cancer is uncertain. Long-term anticoagulation can be discontinued if the risk of recurrent VTEs lowers. In an ambulatory cancer patient in remission with decreased VTE risk factors and not on chemotherapy, low-dose extended treatments may help prevent recurrence [59]. Extended anticoagulation is crucial for long-term CAT management, especially for patients at high risk of recurrence. Studies have shown that low-dose DOACs like apixaban 2.5 mg twice daily and rivaroxaban 10 mg once daily are effective and safe for secondary prophylaxis. The recent data from the API-CAT trial have indicated that the extended anticoagulation with the reduced-dose apixaban results in effective prevention from recurrent VTE in patients with active cancer as the full-dose regimen with a lower incidence of clinically relevant bleeding [60]. These regimens balance thrombotic risk reduction with bleeding risk, particularly in patients with active malignancy or persistent prothrombotic factors. However, more large-scale, cancer-specific trials are needed to refine dosing and patient selection [52,61]. Panel members from cardiovascular surgery have recommended that extended anticoagulation be considered after evaluating the patient's disease dynamics, risk factors, and medications. Some experts believe that extended treatments are necessary to prevent recurrence if the cancer patient has no risk factors or has not experienced bleeding [39]. Panel members from oncology have underlined that physicians should collectively consider the cancer type, predicted prognosis, results of regular thrombosis and bleeding risk assessments (VTE-BLEED score, CAT-BLEED score), comorbidities, cancer status, increase in the treatment cost, as well as patient preferences while deciding on performing indefinite anticoagulation.

LMWH or DOACs can be preferred in prolonged treatment lasting longer than 6 months. Treatment costs, challenges with the subcutaneous route, decreased compliance, and customization of anticoagulation according to patients' needs should be considered when planning the anticoagulation [62].

An annual evaluation of extended treatment is necessary. Factors considered in the evaluation are the completion of antitumor therapy, the cure of cancer, bleeding risk, and survival expectations.

6d. Treatment of VTE recurrence in patients with cancer under anticoagulation

Garfield-VTE found that recurrent VTE was often linked to lung cancer, lymphoma, and pancreatic cancer (12.1% each and 10.6%). Therefore, caution is recommended during the follow-up period as a treatment strategy [54]. First, it should be verified that the patient takes the drugs at the appropriate dose and interval. If no problem is seen in these situations, changes can be made in medical treatment. If LMWH is administered to the patient, a switch to DOACs can be considered, or the LMWH dosage can be increased by 20–25%. If VTE occurs while the patient is on DOACs, a transition to LMWH may be recommended. Following the switch, therapy effectiveness should be closely monitored to assess symptom improvement [63].

6e. Reversal strategies for DOAC-related bleeding

Idarucizumab rapidly reverses dabigatran, and andexanet alfa is used for factor Xa inhibitors like apixaban and rivaroxaban [64,65]. Awareness of these agents is crucial, especially in emergencies or for high bleeding risk patients. Non-specific reversal strategies are important when specific agents are unavailable. Four-factor prothrombin complex concentrate can reverse bleeding in apixaban or rivaroxaban patients, with studies supporting its effectiveness in restoring hemostasis [66]. Activated PCC may be used for life-threatening hemorrhages needing rapid reversal. Although evidence is limited, fresh frozen plasma and tranexamic acid can also manage DOAC-related

bleeding diathesis [67]. In patients with dabigatran-associated bleeding, dialysis can be an alternative method for reducing dabigatran concentrations [68].

7. Drug Interactions

One of the challenges of managing cancer patients who require anticoagulation is the potential drug-drug interactions (DDIs) between antineoplastic agents and anticoagulation. DOACs are increasingly used as an alternative to LMWHs for preventing and treating VTE in cancer patients. However, their awareness of the safety and efficacy of antineoplastic drugs affecting their metabolism and distribution is low. The low level of awareness also affects the preferences of physicians [69]. The pharmacokinetics of all DOACs are influenced by the co-administration of drugs that modulate the P-glycoprotein system. The CYP3A4 system metabolizes rivaroxaban and apixaban, and edoxaban at varying rates [70]. When initiating DOAC therapy, evaluating whether the patient is taking strong CYP3A or P-glycoprotein inhibitor drugs is critical. DOACs have variable degrees of DDI with antineoplastic agents, but there is no significant difference between DOAC-DOAC and DOAC-LMWHs regarding DDI [71]. Verso et. al. found no significant impact of anticancer agents on the efficacy and safety of anticoagulant treatments, including apixaban and dalteparin, in cancer-associated VTE [72]. Apixaban showed no interactions with anticancer therapies, even those involving P-glycoprotein and/or CYP3A4 modulators. This supports its use in patients with cancer-associated VTE undergoing anticancer treatment [71].

Enzalutamide and apalutamide are antiandrogens used for prostate cancer treatment. They induce CYP3A4, CYP2C19, CYP2C9, and P-glycoprotein. Their pharmacological characteristics may impair the efficacy of DOACs, so the concomitant use of these hormonal agents with DOACs is contraindicated [73,74]. Contrary to the common opinion, DOACs can be used except for the strong CYP3A4 and p-glycoprotein inducers mentioned above.

CONCLUSION

CAT is a complex condition that significantly impacts patient outcomes. Advances in risk assessment and anticoagulant therapies, including DOACs, have enhanced management but necessitate individualized approaches due to bleeding risks and drug interactions. Future research focusing on understanding CAT mechanisms, refining risk stratification, and optimizing therapeutic strategies is needed. A multidisciplinary approach is crucial for improving patient care and quality of life.

Article Highlights

- Oncology patients should be evaluated individually (e.g., bleeding profile, presence of distant metastasis, survival time, history of previous major surgery, chemotherapeutics used, etc.), and the medical/endovascular treatment should be determined after the benefit/risk assessment.
- The choice and timing of anticoagulation (AC) should be tailored to the needs of patients with CAT.
- There should be strong collaboration between the medical oncology and cardiovascular surgery departments when following up with CAT patients.
- CAT awareness should be increased among physicians treating oncology patients. For example, when there is a sudden deterioration in the clinical picture of a lung cancer patient who has been responsive to the oncological treatment, CAT should be considered in the differential diagnosis.
- Expert opinions are more valuable in the medical approach of CAT in fragile oncology patients. The Turkish Expert Panel recommends that additional patient characteristics (short survival, bleeding risk, etc.) should be considered in fragile patients and that clinical conditions should not be compelled.
- The 2021 Türkiye National Treatment Guideline for Peripheral artery and vein diseases recommends that "Apixaban may be preferred agent in carefully selected patients with gastrointestinal system tumors".
- For oncology patients to be highly compliant with CAT treatment, the AC agent for the initial treatment should be potent, compatible with the patient's oncologic disease characteristics, and have a safe profile. Considering these, apixaban stands out among available ACs.
- To prevent the development of CAT, all oncology patients, especially those with active diseases, should be followed dynamically and with repeated risk assessment models (RAMs).

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