Primary Prevention of Cancer-Associated Thrombosis: Current Perspectives

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Abstract

Over the past two decades, the incidence of cancer-associated thrombosis (CAT) has increased. It is nowadays a common and often serious complication among patients with cancer. Although medical thromboprophylaxis is recommended for most surgical and nonsurgical cancer patients, it has been infrequently used in ambulatory patients with cancer because of the burden of treatment and concerns about bleeding. However, various risk assessment scores are now available and randomized placebo-controlled trials have established the efficacy of low-molecular-weight heparin or the direct oral Xa inhibitors rivaroxaban and apixaban in ambulatory patients with cancer at high risk of venous thromboembolism (VTE). This review provides an overview of (1) primary thromboprophylaxis in the setting of hospitalized surgical and medical patients, (2) extended thromboprophylaxis after hospital discharge, (3) performance of risk assessment tools for CAT, and (4) primary thromboprophylaxis in ambulatory patients with cancer. The aim is to provide support to physicians in identifying ambulatory patients with cancer at high VTE risk who benefit most from medical thromboprophylaxis according to current recommendations from international guidelines.

Keywords
- cancer
- thrombosis
- prophylaxis
- ambulatory patients
- anticoagulants

Zusammenfassung

In den letzten zwei Jahrzenten wird eine Zunahme der Inzidenz von venösen Thromboembolien (VTE) bei Patienten mit Tumorerkrankung beobachtet. Patienten mit Krebserkrankung weisen neben dem Thromboserisiko ein erhöhtes Risiko für Blutungen auf. Während die medikamentöse Thromboseprophylaxe bei an Krebs erkrankten Patienten nach größeren tumorchirurgischen Eingriffen etabliert ist und bei hospitalisierten Tumorpatienten mit akut internistischen Erkrankungen und Immobilisierung empfohlen wird, stellt die Frage nach primärer Thromboseprophylaxe bei ambulanten Tumorpatienten weiterhin eine klinische Herausforderung dar. Mittlerweile stehen eine Vielzahl an VTE-Risikovorhersagemodellen zur Verfügung, die eine objektive Einschätzung des individuellen VTE-Risikos ermöglichen mit dem Ziel, Patienten mit hohem

Schlüsselwörter
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- Thrombose
- Thromboseprophylaxe
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Risiko zu identifizieren, die von einer medikamentösen Thromboseprophylaxe profitieren. In den letzten Jahren wurden bei Patienten mit hohem VTE-Risiko Studien durchgeführt, die niedermolekulares Heparin bzw. die oralen Xa-Inhibitoren Apixaban und Rivaroxaban gegenüber Placebo verglichen haben.
Dieser Artikel gibt einen Überblick über aktuelle Empfehlungen zur medikamentösen Thromboseprophylaxe nach größeren operativen Eingriffen sowie bei hospitalisierten internistisch kranken Tumorpatienten. Der Fokus des Artikels liegt auf der Primärprophylaxe bei ambulanten Tumorpatienten. Anhand von VTE-Risikovorhersagemodellen sowie den Empfehlungen aus aktuellen Leitlinien wird dargestellt, welche ambulanten Tumorpatienten von einer Thromboseprophylaxe profitieren und wie diese durchgeführt werden kann.

Introduction

Patients with cancer are at increased risk for venous (VTE) and arterial thromboembolism. Over the last two decades, the incidence of cancer-associated VTE has increased threefold, which may be explained by the widespread usage of systemic anticancer treatment, regular computed tomography scans, and improved overall survival.[1] For example, targeted therapy and immunotherapy are now the cornerstone for a broad range of cancers and hematologic neoplasms, but they have been linked to the development of thromboembolism.[2] Besides these treatment-related factors, the risk of cancer-associated thrombosis (CAT) is also driven by cancer- and patient-specific risk factors. For example, patients with pancreatic, lung, brain, ovarian, and stomach cancer are at particularly high risk of VTE.[1,3] Advanced cancer is associated with a higher risk than localized disease and VTE risk is higher in patients with high-grade tumors than in patients with low-grade tumors.[4] Patient-specific factors that increase VTE risk include prior VTE, advanced age, comorbidities, and obesity. Recently, a meta-analysis showed that heritable risk factors, especially non-O blood type, factor V Leiden, and prothrombin G20210A mutation are important genetic risk factors for VTE in patients with cancer.[5]

Thromboembolism is a leading cause of death in patients with cancer and also frequently leads to morbidity. It can be a burden for patients with cancer, as it requires anticoagulation treatment, impairs quality of life, and may result in hospitalization and delays in cancer treatment. In addition, the development of VTE is also an indicator of a more advanced and/or aggressive tumor.[6–8] Patients with CAT have a worse prognosis than cancer patients without thrombosis.[9–11]

Besides the increased VTE risk, patients with cancer are also at increased risk of bleeding complications, even in the absence of antithrombotic medication. Specifically, the bleeding risk is increased in patients with luminal gastrointestinal or genitourinary tract cancers who receive anticoagulation. Patients with glioblastoma or intracranial metastases of renal cell cancer or melanoma also have a high risk of spontaneous hemorrhage.[12,13] Specific anticancer treatments, such as antiangiogenic monoclonal antibodies (bevacizumab, ramucirumab), are associated with a significant increase in bleeding risk.[14] Higher age, low body mass index, anemia, thrombocytopenia, and comorbidities (e.g., arterial hypertension, chronic kidney disease, and prior gastrointestinal bleeding) are other well-known risk factors for bleeding in patients with cancer under anticoagulation.[15,16]

Given the significant mortality and morbidity associated with CAT, many efforts have been made to prevent this complication in vulnerable oncological patients. The risk–benefit ratio, balancing the risks of thrombosis and bleeding, is of utmost importance when deciding about primary thromboprophylaxis.

In this review, we will summarize the best available evidence and recommendations from current international guidelines with regard to hospitalized and ambulatory patients with cancer. In section "Thromboprophylaxis in Ambulatory Patients with Cancer," we will present a patient's case, and at the end of this review, we will describe our decision-making.

Update on Prophylactic Anticoagulation in Nonambulatory Patients with Cancer

Abdominal or pelvic cancer surgery is a well-known VTE risk factor in patients with cancer.[17] In hospitalized medically ill patients, an analysis of the MEDENOX study showed that the presence of cancer or an acute infectious disease, previous history of VTE, and age older than 75 years are independent risk factors for VTE in hospitalized medically ill patients.[18] Among cytotoxic chemotherapy agents applied in hospitalized patients, cisplatin-based chemotherapy regimens and treatment with L-asparaginase in patients diagnosed with acute lymphoblastic leukemia are significantly associated with increased VTE risk.[19,20]

Another important aspect to consider in hospitalized patients with cancer is the end-of-life setting. Data from a prospective observational study in five specialist palliative care units in England, Wales, and Northern Ireland including 273 participants with evaluable ultrasound scans showed that femoral DVT was diagnosed in approximately one-third of patients with advanced cancer within 48 hours after admission to palliative care units. Notably, the incidence of new thrombosis during the 3-week follow-up was low.[21]

Data from a population-based cohort study in the United States revealed that about 75% of all VTE events occur after hospital discharge.[22]

Hence, the evaluation of the need for thromboprophylaxis in nonambulatory patients with cancer is required in three different settings: (1) hospitalized surgical patients, (2) hospitalized medical patients, and (3) extended thromboprophylaxis after hospital discharge for both medical and surgical patients.

1. Cancer surgery increases the risk for VTE about twofold compared to noncancer surgery.[23] A meta-analysis of randomized controlled trials (RCT) recently showed that patients with cancer undergoing surgery with pharmacological in-hospital thromboprophylaxis had a lower risk of deep vein thrombosis (DVT) compared to those not receiving prophylaxis (0.5 vs. 1.2%; RR, 0.51; 95% confidence interval [CI], 0.27–0.94), but a significantly increased risk of all bleeding events (RR, 2.51; 95% CI, 1.79–3.51) and of bleeding events that needed reoperations (RR, 2.92; 95% CI, 1.17–7.28). Notably, there was no difference in the incidence of pulmonary embolism and VTE-related mortality.[24] Based on these RCTs and according to international guidelines, a 4-week course of low-molecular-weight heparin (LMWH) prophylaxis is standard of care after major abdominal or pelvic surgery (laparoscopy or laparotomy).[25–28]
   Recently, two RCTs evaluated direct oral anticoagulants (DOACs) for extended thromboprophylaxis after cancer surgery.[29,30] PROLAPS-II compared rivaroxaban versus placebo in patients undergoing laparoscopic surgery for colorectal cancer.[29] Patients received a standard antithrombotic prophylaxis with LMWH after surgery and were then randomized to receive either rivaroxaban 10 mg once daily or placebo, which was started at 7 ± 2 days after surgery and was continued for 3 weeks. The primary study outcome (composite of symptomatic or asymptomatic ultrasonography-detected DVT, or VTE-related death at 28 ± 2 days after surgery) occurred in 11 of 282 patients in the placebo group compared with 3 of 287 in the rivaroxaban group (3.9 vs. 1%; odds ratio [OR], 0.26; 95% CI, 0.07–0.94). Hence, rivaroxaban was more effective than placebo for extended prevention of VTE, while it was not associated with a significantly increased risk of major bleeding. Guntupalli et al conducted a multicenter randomized trial to investigate the safety and efficacy of apixaban in postoperative patients with suspected or confirmed gynecologic cancer.[30] A total of 400 women were randomized to receive either oral apixaban 2.5 mg twice daily or subcutaneous enoxaparin 40 mg once daily for 28 days after surgery. There were no differences between the apixaban and enoxaparin groups concerning major bleeding (0.5 vs. 0.5%; OR, 1.04; 95% CI, 0.07–16.76), clinically relevant nonmajor bleeding (5.4 vs. 9.7%; OR, 1.88; 95% CI, 0.87–4.1), and VTE (1.0 vs. 1.5%; OR, 1.57; 95% CI, 0.26–9.5). The authors concluded that apixaban may offer a safe and less burdensome alternative to enoxaparin. Based on these two RCTs, the guideline of the American Society of Clinical Oncology (ASCO) was updated in 2023 and now includes a weak recommendation that apixaban or rivaroxaban can be used as an alternative to LMWH for 4 weeks after cancer surgery in patients with low bleeding risk.[28]
2. So far, no dedicated thromboprophylaxis trials specifically in hospitalized patients with cancer have been conducted. The recommendations on inpatient thromboprophylaxis with LMWH or fondaparinux are derived from studies that included hospitalized acutely ill medical patients with only a small proportion of patients with cancer.[31–33] Nonetheless, according to the updated ASCO guidelines, hospitalized patients who have active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.[28]
   Moreover, in hospitalized patients with testicular cancer receiving cisplatin-based chemotherapy, the German S3 guideline and the guideline of the European Association of Urology (EAU) recommend medical thromboprophylaxis, particularly if other risk factors are present (e.g., metastatic disease).[34,35]
   For information on the prevention of asparaginase-related VTE in adults, we refer to the Guidance from the Scientific and Standardization Committee on Hemostasis and Malignancy of the International Society on Thrombosis and Haemostasis (ISTH).[36]
   Patients with advanced cancer and a life expectancy of less than 3 months were generally excluded from studies evaluating medical thromboprophylaxis. Given the lack of data and the uncertain potential benefit of thromboprophylaxis in these patients (as shown by White et al), medical thromboprophylaxis should be critically evaluated in patients with advanced cancer hospitalized in palliative care units.[21]
3. A systematic review and meta-analysis on extended thromboprophylaxis was performed for hospitalized medical patients (cancer and noncancer) and compared DOACs with standard LMWH prophylaxis. DOAC-extended prophylaxis was associated with a significant reduction in the rates of any VTE, including screening-detected asymptomatic events (4.3 vs. 5.61%; RR, 0.76; 95% CI, 0.67–0.87) as well as symptomatic VTE compared to patients receiving LMWH (1.11 vs. 1.8%; RR, 0.66; 95% CI, 0.51–0.86). However, extended-course DOAC led to a significant increase in bleeding compared with LMWH (RR, 1.74; 95% CI, 1.05–2.90). The number of patients needed to treat (NNT) to prevent one VTE was 76 compared to the number needed to harm of 60. Thus, DOACs provide only a small risk reduction in VTE in this patient population comprising both cancer and noncancer patients at the cost of significantly increased bleeding.
   To evaluate extended thromboprophylaxis specifically in patients with cancer, Osataphan et al conducted a systematic review and meta-analysis including four RCTs.[37] LMWH was used for extended thromboprophylaxis in two trials (EXCLAIM and APEX), and rivaroxaban was compared to enoxaparin (MAGELLAN) or placebo

(MARINER).[38–41] In summary, extended thromboprophylaxis in these patients increased the risk of bleeding (OR, 2.10; 95% CI, 1.33–3.35) and was not associated with a significantly reduced rate of VTE events (OR, 0.85; 95% CI, 0.61–1.18). Therefore, recently updated guidelines do not recommend extended thromboprophylaxis after hospital discharge in nonsurgical patients with cancer.[27,28]

Thromboprophylaxis in Ambulatory Patients with Cancer

Data from a large retrospective, observational cohort study on the incidence of VTE in inpatients and outpatients with cancer ($n = 17{,}874$) conducted in the United States showed that 80% of all VTE in patients with cancer occur in the outpatient setting. VTE was an independent predictor of hospitalization and higher hospital costs.[42] With regard to data from Germany, published in a report of the Robert Koch Institut, cancer treatments are by now predominantly given as outpatient-based regimens.[43] Although thromboprophylaxis is well established in hospitalized surgical and medically ill patients with cancer, routine thromboprophylaxis is not recommended for all ambulatory cancer patients because of the modest number NNT and concerns about bleeding. Identification of high-risk ambulatory patients with cancer who benefit from primary thromboprophylaxis is of importance. However, the heterogeneity of the cancer population, new developments in potentially prothrombotic cancer treatments, and individual VTE risk factors pose a challenge when deciding about thromboprophylaxis to ambulatory patients with cancer.

We will discuss the considerations and challenges of thromboprophylaxis based on a brief case presentation. A step-by-step approach to evaluate thromboprophylaxis in this patient case will be presented at the end of this review.

Case

A 63-year-old male patient is diagnosed with locally advanced ductal adenocarcinoma of the pancreatic head. Multiple liver metastases were detected during the staging workup. The patient is in a good Eastern Cooperative Oncology Group (ECOG) performance status (0). His body mass index is 32 kg/m^2. Arterial hypertension was diagnosed a few years ago. The blood count revealed an elevated number of leucocytes (12,500/µL) and thrombocytes (412,000/µL) and low hemoglobin (11 g/dL). He is offered palliative systemic chemotherapy with the modified FOLFIRINOX protocol including oxaliplatin, leucovorin, irinotecan, and fluorouracil. Implantation of a central venous access device (subcutaneous port) is planned. As advanced pancreatic adenocarcinoma is frequently associated with thromboembolic events, the question arises whether primary thromboprophylaxis should be considered in this patient in the ambulatory setting.

VTE Risk Assessment Models in Ambulatory Patients with Cancer

The goal of primary thromboprophylaxis is to reduce the risk of VTE and prevent burdensome short- and long-term sequelae. The challenge is to identify patients with a high risk of VTE who will most likely benefit from thromboprophylaxis when systemic chemotherapy is initiated. Therefore, various risk assessment tools have been developed of which the Khorana score is best known. This score was introduced in 2008 and combines five clinical and laboratory variables to stratify patients into low-, intermediate-, and high-risk categories (►Table 1).[44] In a meta-analysis including over 34,000 patients, the 6-month incidence of VTE was 5.0% (95% CI: 3.9–6.5) in patients with a low-risk Khorana score (0 points), 6.6% (95% CI: 5.6–7.7) in those with an intermediate-risk Khorana score (1 or 2 points), and 11.0% (95% CI: 8.8–13.8) in those with a high-risk Khorana score (≥ 3 points).[45] Of note, this classification had a poor sensitivity with only 23% of the patients who developed VTE in the first 6 months belonging to the high-risk group. By lowering the threshold for the high-risk group from 3 to 2 points, the proportion of patients classified as high-risk increased from 17 to 47% while lowering the absolute risk of VTE in this group from 11 to 9%. A Khorana score of ≥ 2 points was used to enroll ambulatory patients with cancer at intermediate to high VTE risk in two large, randomized, placebo-controlled trials on primary thromboprophylaxis with rivaroxaban and apixaban, respectively, and has been included in recently published guidelines.[28,46–49] These trials will be discussed in detail in the following section.

Recently, Li et al derived and externally validated a new risk assessment model for VTE using retrospective data from approximately 90,000 patients with newly diagnosed cancer from the electronic health records of two large health care systems in the United States.[50] The model includes the original components of the Khorana score with revised cancer subtypes, two cancer-specific predictors (advanced stage and targeted/endocrine therapy), and four patient-specific predictors. Using this new risk assessment model, approximately 50% of patients with cancer receiving modern systemic therapy were stratified into a high-risk group with a 6-month VTE risk of 8 to 10%. Therefore, the model showed improved performance over the original Khorana score. An additional external validation from prospective studies has not yet been performed.

With the aim to improve the prediction of CAT, new risk assessment tools have been developed including PROTECHT, ONCOTEV, CONKO, COMPASS, and the new-Vienna CATS model.[51–55] The new-Vienna CATS model is the only tool that provides an individualized estimate of the 6-month VTE risk based on tumor-site category and D-dimer concentrations only (CAT score calculator: https://catscore.shinyapps.io/catscore/).[55] The score was validated in an independent cohort of ambulatory patients with cancer, and also appeared to identify high-risk patients in a post hoc analysis of an RCT.[55,56] Recently, it was demonstrated in a large prospective study of patients initiating chemotherapy for newly diagnosed metastatic non-small cell lung cancer (NSCLC) and colorectal, gastric, and breast cancers that this model has better discrimination than the traditional Khorana score and can effectively identify patients at the highest risk of 6-month mortality.[57]

Table 1 Khorana score

Risk factor			Points
Site of primary tumor			
Very high risk (stomach, pancreas)			2
High risk (lung, gynecologic, bladder, testicular, lymphoma)			1
All other sites			0
Prechemotherapy platelet count (≥350,000/μL)			1
Prechemotherapy hemoglobin level (< 10 g/dL or use of erythropoiesis-stimulating agents)			1
Prechemotherapy white blood count (> 11.000/μL)			1
Body mass index≥35 kg/m^2			1
Incidence of VTE based on Khorana score			
Khorana score points	**Derivation cohort[44] VTE risk after 2.5 months**	**Validation cohort[44] VTE risk after 2.5 months**	**Meta-analysis[45] VTE risk after 6 months**
0 (low)	0.8%	0.3%	5.0%
1–2 (intermediate)	1.8%	2.0%	6.6%
≥ 3 (high)	7.1%	6.7%	11%

Abbreviation: VTE, venous thromboembolism.
Notes: The Khorana score was developed and validated in cancer patients receiving a first course of chemotherapy to predict the cumulative incidence of VTE at 2.5 months. Data from the meta-analysis are derived from 27,849 patients in whom 6-month follow-up data were available.

Parenteral Thromboprophylaxis in Ambulatory Patients with Cancer

In early clinical trials evaluating the effect of pharmacological thromboprophylaxis on VTE, LMWH was used in patients with a broad range of solid tumor types undergoing ambulatory anticancer treatment, without the selection of high-risk patients. The results of the two largest placebo-controlled randomized trials (PROTECHT and SAVE-ONCO) showed that thromboprophylaxis with nadroparin or semuloparin significantly reduced the risk of VTE by 49 to 65%, but the rates of events and the absolute differences were low (nadroparin vs. placebo: 3.9 vs. 2.0%; semuloparin vs. placebo: 1.2 vs. 3.4%) with an NNT of 46 to 50.[51,58–60] In a recent Cochrane meta-analysis comparing thromboprophylaxis with LWMH to no thromboprophylaxis, LMWH was associated with a relative VTE risk reduction of 38% (RR, 0.62; 95% CI, 0.46–0.83) but at the cost of a significantly increased risk of major bleeding (RR, 1.63; 95% CI, 1.12–2.35).[61] Due to concerns about the bleeding, the modest NNT, and the burdensome daily subcutaneous injections, LMWH is rarely used in clinical practice for the prevention of VTE in ambulatory patients with cancer.

Thromboprophylaxis with Direct Oral Xa Inhibitors in Ambulatory Patients with Cancer

DOACs may be preferred for thromboprophylaxis because they can be given orally in fixed doses. The efficacy and safety of the direct oral Xa inhibitors apixaban and rivaroxaban compared to placebo have been studied in the AVERT and CASSINI trials, which had a follow-up duration of 6 months.[47,62] The main characteristics and results are summarized in ►Table 2. Ambulatory cancer patients initiating systemic anticancer therapy with an intermediate-high risk of VTE (based on the Khorana score ≥2) were enrolled. Unlike AVERT, CASSINI implemented a lower limb ultrasound screening in all patients before enrollment as well as every 8 weeks during follow-up. Based on the presence of asymptomatic DVT at baseline, 4.5% of patients were excluded. A meta-analysis of these two trials reported that DOACs were associated with a significant reduction of overall VTE events compared to placebo (RR, 0.56, 95% CI, 0.35–0.89), while the risk of on-treatment major (RR, 1.96, 95% CI, 0.80–4.82) and clinically relevant non-major bleeding (RR, 1.28, 95% CI, 0.74–2.2) was nonsignificantly higher.[63] Compared to the earlier PROTECHT and SAVE-ONCO trials, the absolute risk reduction was two- to threefold higher in the DOACs studies, likely due to the enrolment of high-risk patients in the AVERT and CASSINI trials based on the Khorana score.

According to the international guidelines that were updated in 2022/2023 (guidelines from ASCO, European Society of Medical Oncology [ESMO], and the International Initiative on Cancer and Thrombosis [ITAC]), a VTE risk assessment should be performed in ambulatory patients initiating first-line systemic anticancer therapy by using validated risk assessment models.[27,28,49] Patients at intermediate to high risk of VTE (Khorana score ≥2) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided that there are no contraindications.[27,28] Of note, the ESMO guidelines suggest an estimated risk of VTE of >8 to 10% as the threshold for discussion of primary thromboprophylaxis and refer to the calculation of the individual risk by using the Vienna-CATS nomogram score and the COMPASS-CAT score.[27] The ITAC guideline recommends

Table 2 CASSINI and AVERT trials

	CASSINI	AVERT
Main characteristics		
Anticoagulant	Rivaroxaban	Apixaban
Dosage	10 mg OD	2.5 mg BID
Patients at randomization	841	563
Screening ultrasound for DVT	Yes	No
Primary tumor type (selection) (%)		
Brain	[a]	4.1
Bladder	[b]	0.9
Breast	2.1	Not specified
Colon	[c]	1.9
Gastric/gastroesophageal junction	20.9	7.7
Gastrointestinal (other)	3.1[d]	Not specified
Genitourinary	3.8[e]	Not specified
Gynecologic	5.4[f]	25.6
Lung	15.9	10.3
Lymphoma	7.0	25.2
Myeloma	[a]	2.6
Ovarian	6.4	Not specified
Testicular	[b]	0.6
Pancreas	32.6	13.6
Prostate	[g]	0.4
Others	2.7[i]	7.2
Mean intervention period (months)	4.3	5.2
Results		
VTE (%)	R: 6.0 vs. P: 8.8	A: 4.2 vs. P: 10.2
Hazard ratio (95% CI)	0.66 (0.4–1.09)	0.41 (0.26–0.65)
On-treatment VTE (%)	R: 2.6 vs. P: 6.4[i]	A: 1.0 vs. P: 7.3[i]
Hazard ratio (95% CI)	0.40 (0.20–0.80)	
NNT-VTE on treatment	26[i]	16[i]
Major bleeding (%)	Not specified	A: 3.5 vs. P: 1.8
Hazard ratio (95% CI)		2.0 (1.01–3.95)
On-treatment major bleeding (%)	R: 2.0 vs. P: 1.0[i]	A: 2.1 vs. P: 1.1[i]
Hazard ratio (95% CI)	1.96 (0.59–6.49)	
Mortality	R: 21.0 vs. P: 26.2	A: 12.2 vs. P: 9.8[i]
NNH on-treatment	101[i]	100[i]

Abbreviations: A, apixaban; BID, twice daily; DVT, deep vein thrombosis; NNT, number needed to treat; NNH, number needed to harm; OD, once daily; P, placebo; R, rivaroxaban; VTE, venous thromboembolism.
Notes: The CASSINI and AVERT trial enrolled patients with a Khorana score of ≥ 2 who were starting chemotherapy to receive rivaroxaban/apixaban or placebo for 180 days.[46,47]
[a]Excluded.
[b]Included in genitourinary cancers.
[c]Included in other gastrointestinal cancers.
[d]Other gastrointestinal cancers include esophageal, cholangiocarcinoma, gallbladder liver, colorectal, peritoneal, and anal.
[e]Genitourinary cancers included renal, bladder, ureteral, and testicular cancers but not prostate cancer.
[f]Other gynecologic cancers include cervical, uterine, vulvar, endometrial, and fallopian tube.
[g]Included in "others."
[h]Others include head and neck cancers, prostate, mesothelioma, melanoma, unknown primary, and sarcomas.
[i]88

the use of apixaban and rivaroxaban in this situation.[49] Additionally, the ASCO guideline points out that patients should receive educational material on CAT.[28]

Thromboprophylaxis in Selected Patients with Cancer

Various RCTs have evaluated thromboprophylaxis in selected cancers that are associated with a high risk of VTE, including pancreatic, gastroesophageal, and lung cancer. Such an approach reduces the heterogeneity in the studied population, allows for studying a high-risk group without the need for risk assessment tools, and aligns well with the current trend of oncologists specializing in a single-cancer type.

Patients with *pancreatic cancer* have a particularly high risk of VTE. A recent retrospective cohort study including 400 patients with metastatic pancreas cancer reported a VTE incidence of 17.5% with a median time of occurrence of 3.5 months after diagnosis. Noteworthy, patients affected by VTE had a lower median overall survival compared to patients without VTE (10.5 vs. 13.4 months).[64] Therefore, specific clinical trials comparing LMWH to placebo have been performed in individuals with metastatic or locally advanced pancreatic cancer, including the FRAGEM and CONKO-004 trials.[52,65] It is worth emphasizing that dalteparin and enoxaparin were used in therapeutic and half-therapeutic dosages, respectively. The VTE rate was reduced by more than 80% without a significant increase in bleeding complications. Patients with pancreatic cancer were examined in a subgroup analysis of the CASSINI trial. During the intervention period, rivaroxaban significantly reduced the risk of VTE compared to placebo (3.7 vs. 10.1%; hazard ratio [HR] = 0.35, 95% CI: 0.13–0.97) without increasing the risk of major bleeding.[66] A meta-analysis assessing the efficacy and safety of thromboprophylaxis in pancreatic cancer patients has recently been published. Data were retrieved from five RCTs including the subgroup analysis of the CASSINI trial. Compared to placebo, thromboprophylaxis significantly decreased the risk of VTE (pooled RR: 0.31, 95% CI: 0.19–0.51) with an estimated NNT of 12 patients to prevent one VTE. Similar results were observed in studies with parenteral versus oral anticoagulants and in studies using different dosages of LMWH.[67]

Due to the particularly high risk in patients with pancreatic cancer and the comparatively low bleeding risk, the ESMO guideline states that for ambulatory pancreatic cancer patients on first-line systemic anticancer treatment, LMWH at a higher dose (150 IU/kg dalteparin or 1 mg/kg enoxaparin once daily) may be considered for a maximum of 3 months.[27] Notably, the recommendation regarding higher doses of LMWH applies only to patients with pancreatic cancer. If indicated, LMWH should be used in standard prophylactic doses in patients with other cancer types associated with a high risk for VTE.

The high risk of VTE in patients with *NSCLC* and *gastrointestinal cancers* is well established.[1] Specific genetic alterations (especially the presence of ALK/ROS1 translocations) and anticancer treatment with chemo-based regimens and chemo-based regimens in combination with immune checkpoint inhibitors further increase the thromboembolic risk in patients with NSCLC.[68,69] In particular, a high risk of VTE was reported in several trials investigating amivantamab, a bispecific EGFR and MET receptor antibody, in patients with NSCLC compared with control therapy.[70] In a recently published study including 328 patients with lung or gastrointestinal cancer, VTE risk stratification (low vs. high risk of VTE) was based on D-dimer and fibrinogen levels. High-risk patients ($n = 200$; 61%) commencing anticancer treatment were randomized to receive enoxaparin 40 mg once daily for 90 days or no thromboprophylaxis.[71] The primary outcome was confirmed VTE at 180 days, which occurred in 8 (8%) individuals randomized to enoxaparin and in 23 patients (23%) of the control group (HR: 0.31; 95% CI: 0.15–0.70) with an NNT of about 7. The rate of major bleeding was low (1% in the high-risk group randomized to enoxaparin and 2% in the high-risk control group). The number of patients with lung cancer in the CASSINI and AVERT trials was too small to allow for an adequately powered subgroup analysis, whereas the proportion of patients with gastric/gastroesophageal junction tumors was 20.9% in the CASSINI and 7.9% in the AVERT trial.[46,47] In a subgroup analysis of these patients of the CASSINI trial, the VTE rate was 3.4% in patients treated with rivaroxaban versus 6.9% in those receiving placebo (HR: 0.45; 95% CI: 0.11–1.8); the corresponding rates for major bleeding were 4.6 versus 1.2%, respectively (HR: 3.77; 95% CI: 0.42–33.73).[72] Efficacy and safety of apixaban in patients with gastrointestinal cancers were examined in a post hoc analysis of the AVERT trial.[73] The cancer types included in this group were upper gastrointestinal, pancreas/hepatobiliary, and colorectal. VTE occurred in 4.6% of patients in the apixaban group and 20% of patients in the control group (HR: 0.27; 95% CI: 0.13–0.54). The rate of major bleeding was twofold higher in the apixaban versus the placebo group (HR: 2.39; 95% CI: 0.29–19.78), which was driven by bleeding in patients with pancreatic/hepatobiliary cancer; no major bleeding occurred in the patients with upper gastrointestinal or colorectal cancers.

The guidelines do not provide specific recommendations regarding patients with lung and gastrointestinal tumors, except for the ITAC guidelines from 2022, suggesting not to use routine primary prophylaxis in patients with lung cancer.[49]

Thromboprophylaxis in Ambulatory Patients with Multiple Myeloma

Among patients with hematologic neoplasms, those with multiple myeloma are exposed to the highest risk of venous and arterial thrombosis.[1] VTE risk factors are related to pathophysiological changes in the coagulation system, individual comorbidities, and the specific therapy given. Especially immunomodulatory drugs (IMiD), such as thalidomide, pomalidomide, and lenalidomide, in combination with high doses of corticosteroids are associated with a high risk of VTE. Today, lenalidomide-containing triplet and quadruplet therapies are the standard of care.[74] A study on the incidence of VTE during the first year of diagnosis in patients with multiple myeloma undergoing a triplet or quadruplet lenalidomide-based induction therapy reported a VTE rate of 12.4%. The VTE risk was particularly increased in patients receiving the proteasome inhibitor carfilzomib in combination with lenalidomide (21.1%).[75]

Guidelines have traditionally suggested acetylsalicylic acid as thromboprophylaxis for low-risk patients and a vitamin K antagonist for those at high risk based on simple criteria. Recently, two more sophisticated risk assessment tools have been developed that were externally validated (►Table 3). The SAVED score predicts the risk for VTE in patients with multiple myeloma receiving an IMiD.[76] The SAVED score was derived using data from more than 2,300 patients with multiple myeloma within the SEER-Medicare database and validated using data from 1,200 patients with multiple myeloma from the Veterans Administration Central Cancer Registry. In the validation cohort, VTE occurred in 9.4% of patients within 12 months after starting the IMiD therapy. Patients with a SAVED score ≥2 had a higher incidence of VTE after starting IMiD therapy at 3 months (6 vs. 4%), at 6 months (11 vs. 7%), and at 12 months (16 vs. 8%). The IMPEDE VTE score can be applied in patients with multiple myeloma independent of therapy.[77] In the derivation cohort, three risk groups could be determined based on the 6-month cumulative incidence rates of VTE from the start of chemotherapy: ≤3 points, 3% VTE risk; 4 to 7 points, 8.3% VTE risk; ≥8 points, 15.2% VTE risk. Of note, both risk assessment scores were developed before newer agents for the treatment of multiple myeloma were available (i.e., proteasome inhibitors, CD38 antibodies). Moreover, there are limited data regarding over-the-counter use of acetylsalicylic acid in the study population. In summary, patients with multiple myeloma are considered to be at high VTE risk according to a SAVED score ≥2 points and an IMPEDE score of ≥8 points.

According to the latest National Comprehensive Cancer Network guidelines, low-dose acetylsalicylic acid is recommended in low-risk patients, whereas prophylactic dosages of LMWH, fondaparinux, rivaroxaban, apixaban, or warfarin (target INR: 2–3) are recommended in high-risk patients.[78] Since VTE risk is high and so particularly dependent on anticancer therapy, periodic risk assessment is recommended both at the time of diagnosis and during the course of the disease. Trials evaluating the safety and efficacy of thromboprophylaxis with apixaban and rivaroxaban have recently been published.[79]

Steps in Evaluating Primary Thromboprophylaxis in Ambulatory Patients with Cancer

Data from a global online survey on VTE education and awareness among people living with cancer were recently published.[80] In this cross-sectional study, 27 items

Table 3 VTE risk stratification scoring systems in patients with multiple myeloma

Abbreviation	Factors	Points
S	**S**urgery (within 90 days)	+2
A	**A**sian population	−3
V	History of **V**TE	+3
E	**E**lders: Age ≥80 y	+1
D	**D**examethasone > 160 mg/months *or* **D**examethasone 120–160 mg/months	+2 +1
The SAVED score is used to predict the risk of VTE in patients with multiple myeloma receiving an immunomodulatory drug (i.e., lenalidomide, pomalidomide, thalidomide)[76]		
A score of ≥2 designates high VTE risk		
Abbreviation	**Factors**	**Points**
I	**I**mmunomodulatory drug	+4
M	Body **m**ass index ≥25 kg/m^2	+1
P	**P**elvic, hip, or femur fracture	+4
E	**E**rythropoiesis-stimulating agent	+1
D	**D**oxorubicin or multiagent chemotherapy	+3
D	**D**examethasone >160 mg/months *or* **D**examethasone < 160 mg/months	+4 +2
E	**E**thnicity/race: Asian/Pacific Islander	−3
V	History of **V**TE before diagnosis of multiple myeloma	+5
T	**T**unneled central line *or* central venous catheter	+2
E	**E**xisting thromboprophylaxis with prophylactic LWMH or acetylsalicylic acid *or* therapeutic dose LMWH or warfarin	−3 −4
The IMPEDE VTE score is used to predict the risk of VTE in patients with multiple myeloma receiving an immunomodulatory drug (i.e., lenalidomide, pomalidomide, thalidomide) or not within 6 months[77]		
A score of ≥8 designates high VTE risk		

Abbreviations: LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

addressing unmet needs and barriers in VTE education and awareness were analyzed using a quantitative and qualitative approach. The survey revealed that among 2,262 patients with cancer, 55.3% received no VTE education. The vast majority of the participants (78.8%) believed that receiving VTE education is at least very important. The option of primary thromboprophylaxis was discussed only with 40% of the responders. Moreover, a survey in the United States reported that only 9% of oncologists use a structured risk assessment model and a minority of the patients at high risk of VTE receive thromboprophylaxis.[81] These findings highlight the difficulty of implementing guideline recommendations in clinical practice.

Recently, Martin et al used implementation research to address barriers concerning the underuse of primary VTE prophylaxis and to answer the question how the use of primary VTE prophylaxis can be facilitated.[82] The authors identified 12 implementation strategies and important outcomes to evaluate these strategies, such as conducting clinician education and training on risk assessment models and medical thromboprophylaxis as well as the development and distribution of education materials for clinicians and patients.

The results of the study will be used to test and measure the strategies to improve the uptake of evidence-based recommendations for VTE prevention in oncology practice.

To improve awareness and appropriate use of pharmacological thromboprophylaxis in ambulatory patients with cancer, we recommend the following approach with reference to the aforementioned patient case. For a more detailed algorithm for individual decisions for thromboprophylaxis in patients with cancer, we refer to the "Daily practice recommendations by the Hemostasis Working Party of the German Society of Hematology and Medical Oncology, the Society of Thrombosis and Hemostasis Research, and the Austrian Society of Hematology and Oncology."[48]

Case (Continued)

Step 1: Calculating the Risk of VTE by Using Validated Risk Assessment Models

In our case, the Khorana score was calculated to be 4 points (2 points for the cancer type and 1 point each for elevated leucocyte and platelet counts, respectively), corresponding to a high risk of VTE. Using the new-Vienna CATS model (calculated with the patient's D-dimer of 3.5 µg/mL), the predicted 6-month VTE risk is 14.1%.

Step 2: Evaluation of Contraindications to Thromboprophylaxis

Noteworthy, data on the risk of bleeding in patients with cancer is weaker compared to risk factors for VTE, and due to the lack of a validated risk assessment score for bleeding, the individual bleeding risk is hard to predict. However, information should be collected on factors that may influence the individual risk of bleeding and on drug–drug interaction when prophylaxis with rivaroxaban or apixaban is planned. The assessment of the bleeding risk should include the tumor site, the individual bleeding risk, and drug-specific risk factors for bleeding. Increased bleeding risk may be present in patients with endoluminal tumors located in the gastrointestinal or genitourinary tract, in patients with brain tumors (glioma), and in the presence of brain metastases. The medical history should focus on the bleeding history of the patients and on comorbidities that are associated with an increased bleeding risk (e.g., thrombocytopenia with a thrombocyte count $<$50.000/µL, severe renal impairment with a creatinine clearance $<$30 mL/min, uncontrolled arterial hypertension). Different antiangiogenic agents, including monoclonal antibodies (e.g., bevacizumab, ramucirumab), tyrosine kinase inhibitors (e.g., sunitinib, sorafenib), and BTK inhibitors (e.g., ibrutinib) are associated with an increased risk of bleeding. Additionally, attention should be paid to concomitant pain medication (e.g., nonsteroidal anti-inflammatory drugs).[83] Recently, two new risk scores estimating the bleeding risk in patients with CAT have been developed, which require external validation in practice-based settings.[84,85]

In our case, there are no underlying factors that may increase the bleeding risk under medical thromboprophylaxis. Care should be taken to control the patient's blood pressure.

Step 3: Shared Decision-Making

In our case, based on the available evidence, we point out the estimated 6-month VTE risk of about 14% after initiating systemic cancer therapy to the patient and discuss the benefits and risks of thromboprophylaxis. We inform the patient about the advantages and disadvantages of LMWH and oral anti-Xa inhibitors. The patient agrees with thromboprophylaxis and is in favor of an oral anti-Xa inhibitor. We additionally note that DOACs are not approved for primary prophylaxis in ambulatory patients with cancer in Germany. Apixaban (2.5 mg twice daily) is initiated simultaneously with systemic cancer treatment and is planned for a duration of at least 6 months provided that no relevant side effects occur.

Step 4: Patient Education

We instruct the patient to take the tablet correctly and inform about signs of bleeding and thromboembolism.

Step 5: Careful Monitoring

We assess for adherence to the drug, side effects, organ dysfunctions, thrombocytopenia, comorbidities, and comedication at regular intervals.

Conclusion and Future Perspective

In ambulatory patients with cancer, validated risk assessment tools are available to identify patients who are at high VTE risk. The individual VTE risk and risk factors for bleeding should be considered in a stepwise approach to decide whether primary thromboprophylaxis is appropriate for the individual patient. If primary thromboprophylaxis is considered, shared decision-making on the type of anticoagulation (LMWH vs. rivaroxaban/apixaban) is recommended. With the development of anticoagulants targeting FXI and FIXa, the anticoagulation-related bleeding risk may be lower compared to

standard anticoagulants.[86] Trials on the use of FXI/FIXa inhibitors are ongoing and upcoming for different indications for primary VTE and ATE prevention, specifically including patients with cancer (e.g., NCT04465760).[87]

Authors' Contributions

C.H. and M.V. wrote the manuscript. All authors contributed to the manuscript drafting, reviewed the manuscript, and approved the final version.

Conflicts of Interest

C.H. reports honoraria for lectures or consultancy from Bayer, BMS, Pfizer, Sanofi, LEO Pharma. N.v.E. has nothing to disclose. M.V. reports honoraria for lectures or consultancy from BMS and Pfizer and travel grants from Bayer and LEO Pharma.

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