POLISH ARCHIVES OF
Internal Medicine
POLSKIE ARCHIWUM MEDYCYNY WEWNĘTRZNEJ

ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formated version will be made available soon.

Primary prevention of venous thromboembolism in ambulatory cancer patients: recent advances and practical implications

Authors: Amye M. Harrigan, Marc Carrier, Tzu-Fei Wang

Article type: Review article

Received: March 10, 2024.

Revision accepted: April 19, 2024.

Published online: April 25, 2024.

ISSN: 1897-9483

Pol Arch Intern Med.

doi:10.20452/pamw.16739

Primary prevention of venous thromboembolism in ambulatory cancer patients: recent advances and practical implications

Amye M. Harrigan[1,2], Marc Carrier[2], Tzu-Fei Wang[2]

1 Department of Medicine, Dalhousie University, Halifax, NS, Canada

2 Department of Medicine, University of Ottawa at The Ottawa Hospital and Ottawa Hospital Research Institute, Ottawa, ON, Canada

Correspondence to: Tzu-Fei Wang, MD, MPH, The Ottawa Hospital, General Campus 501 Smyth Road, Box 201A, Ottawa, ON K1H 8L6, Canada, phone: 613-737-8899, ext 73755, email: tzwang@toh.ca

Abstract

Venous thromboembolism (VTE) is a common complication in ambulatory cancer patients receiving anticancer therapies. Many patient-, cancer- and treatment-related factors along with specific biomarkers can be associated with an increased risk of VTE in patients with cancer. Risk assessment models such as the Khorana score serve as valuable tools to aid in the identification of patients with cancer who are at high risk of VTE. Two randomized controlled trials have evaluated the efficacy of primary thromboprophylaxis with low-dose direct oral anticoagulants, apixaban and rivaroxaban, to reduce the risk of VTE in ambulatory patients with cancer who are at intermediate to high risk of VTE identified by the Khorana score. This narrative review summarizes the literature on the risk factors and risk assessment process for VTE and the use of primary thromboprophylaxis in ambulatory cancer patients. We also

outline important practical considerations for initiating primary thromboprophylaxis in this population.

Key words

ambulatory, anticoagulation, cancer-associated thrombosis, prevention, thromboprophylaxis

Introduction

Cancer-associated thrombosis (CAT), most commonly encompassing pulmonary embolism (PE) and both upper and lower extremity deep vein thrombosis (DVT), is a common complication in patients with cancer. Compared to the general population, patients with cancer have a risk of venous thromboembolism (VTE) up to 12-fold higher at 6 months [1]. This increased risk can be up to 23-fold higher in patients receiving systemic anticancer therapies [1]. Thromboembolism is the second leading cause of death in individuals with cancer, and it also significantly impacts morbidity, prognosis, treatment timelines, healthcare resource utilization, and overall quality of life for patients and their families [2-4]. Over the past two decades, CAT incidence has risen at least 3-fold, and it occurs frequently in ambulatory patients [1]. Primary thromboprophylaxis, aimed at mitigating the risk of initial VTE events, proves beneficial for select high-risk individuals with cancer [5,6]. This review aims to delineate common risk factors of VTE in patients with cancer, provide guidance on who should be considered for primary thromboprophylaxis, and highlight important factors to consider when initiating pharmacological thromboprophylaxis.

Risk factors for cancer-associated thrombosis

Numerous factors contribute to CAT risk and can be broadly categorized as patient-related, tumor-related, and treatment-related factors as well as the presence of specific biomarkers [2,7,8]. An overview of the different risk factors is shown in Figure 1.

Patient-related factors Pertinent patient-related risk factors include advanced age, previous VTE, family history of VTE and the presence of medical comorbidities such as cardiovascular risk factors [2,9]. Extremes of body weight have also been reported to influence VTE risk with both low (<18.5 kg/m^2) and high (≥35 kg/m^2) body mass index (BMI) being associated with an increased incidence of CAT [9]. Recently, inherited thrombophilia such as Factor V Leiden as well as non-O blood type have also been associated with an increased risk of CAT [2,10,11].

Tumor-related factors Tumor type can significantly influence the risk of CAT. Gastrointestinal cancers such as esophageal, gastric, hepatobiliary, and pancreatic cancers are among the most frequently reported cancers to be associated with CAT [1,2]. Other tumor types that could be associated with high risk of CAT include brain, genitourinary, lung and some hematologic malignancies [1,2]. In addition, high histologic tumor grade (i.e., Grade 3 or 4 as per the American Joint Committee on Cancer group-level grading system), regionally advanced or metastatic cancer, vascular compression from tumor and time since diagnosis are associated with a higher risk of CAT [2,8,12,13].

Treatment-related factors Systemic anticancer therapies are an important risk factor for CAT. A population-based study from the United States reported that, compared with patients without cancer, patients with cancer not receiving chemotherapy had an odds ratio (OR) of 4.1 (95% confidence interval [CI] 1.9 to 8.5) for CAT, whereas patients receiving chemotherapy had an OR of 6.5 (95% CI 2.1 to 20.2) [14]. Platinum-based chemotherapy and anti-angiogenesis treatments (e.g., bevacizumab) are frequently associated with VTE [2,15,16]. Other treatments associated with VTE in patients with cancer include immunomodulatory agents (e.g., thalidomide, lenalidomide), immune checkpoint inhibitors, hormonal therapy, and erythropoiesis-stimulating agents [2,17]. Major cancer surgeries are

also associated with an increased risk of VTE. Additionally, some evidence suggests an association between radiation therapy and VTE in patients with cancer [2]

Biomarkers The improved understanding of the mechanisms of CAT has led to the identification of several biomarkers that correlate with the occurrence of VTE in cancer [18]. These mechanisms can be categorized into 1) expression of proteins by tumors that can alter host systems and 2) tumor expression of procoagulant proteins that are released into circulation and activate platelets or / and the coagulation cascade [18]. For example, different tumor types can increase the number of platelets and leukocytes in the circulation leading to the formation of neutrophil extracellular traps (NETs), which promote VTE by trapping platelets, red blood cells and extracellular vesicles (EV) with tissue factor (TF) activity [19,20]. As for examples of procoagulant proteins released by tumors, these include EV containing TF, polyphosphate, or podoplanin (PDPN) [18,19]. Extracellular vesicles containing TF can activate the clotting cascade, polyphosphate-containing EV can activate factor XIl (FXII) and platelets, and PDPN- containing EVs can activate platelets. Certain tumors can also release plasminogen activator inhibitor 1 (PAI-1), which in turn inhibits fibrinolysis [18,19].

Hematologic parameters such as increased leukocyte and/or platelet counts as well as decreased hemoglobin have been shown to be reliable predictors of VTE risk in patients with cancer and have been integrated into risk prediction models to identify patients with cancer who are at an increased risk of VTE [21-24]. Other biomarkers such as elevated concentrations of prothrombin fragment 1+2, soluble P-selectin, NETs, TF, PDPN, PAI-1, Factor VIII and D-dimer have also been identified as predictors of increased VTE risk in individuals with cancer [19,25,26,27]. However, the use of these biomarkers in clinical practice remains limited as most of them are not as routinely available.

Identifying patients with cancer who are at high risk of cancer-associated VTE

The high rate of VTE in patients with cancer and its significant impact on morbidity and mortality have sparked interests in the use of anticoagulants as primary VTE prophylaxis. The first few randomized controlled trials (RCTs) evaluating thromboprophylaxis in ambulatory patients with cancer compared heparin derivatives to placebo in patients with a range of solid tumor types (e.g., lung, breast, ovarian, head and neck, gastrointestinal, pancreatic) and specifically in patients with advanced pancreatic cancer [28-32]. These studies reported that primary thromboprophylaxis with heparin derivatives significantly reduced the risk of VTE compared with placebo, but there was a non-significantly increased risk of major bleeding [28-32]. In a recent systematic review and meta-analysis, compared to no thromboprophylaxis, low-molecular-weight heparin (LMWH) was found to reduce the incidence of symptomatic VTE (relative risk [RR] 0.62, 95% CI 0.46 to 0.83) but increase the risk of major bleeding events (RR 1.63, 95% CI 1.12 to 2.35) [33]. Despite the decreased rate of VTE with primary LMWH thromboprophylaxis, its routine use in ambulatory cancer patients was not widely adopted or recommended in guidelines from major societies and organizations [34-39]. Frequently cited reasons included that the absolute VTE risk reduction was modest (i.e., 0.8–2.4%), resulting in a relatively high number needed to treat (NNT of >100), the concerns of increased risks of bleeding, as well as the inconvenience and potentially high costs of daily subcutaneous injections [8].

To improve upon the above-mentioned limitations, various risk prediction models have been proposed to identify patients with cancer who are at higher risk of VTE, as targeting high-risk patients may improve the risk-benefit balance. These risk models incorporate various patient-, tumor-, treatment-related factors and select biomarkers to predict the risk of VTE and stratify patients according to their risk of future VTE event [21-23,40,41]. The most widely used and validated risk prediction model is the Khorana risk assessment

model [21,42]. The Khorana score incorporates five parameters: site of primary cancer, BMI $\geq$35 kg/m^2, pre-chemotherapy platelet count $\geq$350x10^9/L, pre-chemotherapy leukocyte count >11x10^9/L, and hemoglobin <10 g/dL or the use of an erythrocyte stimulating agent (Table 1) [21]. Each parameter is assigned 1 point, except for the site of primary cancer, where very high-risk cancers such as stomach and pancreas are assigned a score of 2 and other high-risk cancers such as lung, lymphoma, gynecological, bladder or testicular are assigned a score of 1 [21]. In the original cohort, a score of 0 indicated low risk of VTE, a score of 1–2 indicated intermediate VTE risk and a score of 3 or more indicated high risk of VTE, corresponding to rates of VTE over a median follow-up of 2.5 months being 0.8%, 1.8% and 7.1%, respectively [21]. Similar rates of VTE were observed in the validation cohort [21].

Since publication, the Khorana score has been retrospectively and prospectively validated in over 100 000 patients in various oncologic settings [43,44]. A prospective validation study conducted by the Vienna group found that patients with cancer and a Khorana score of 2 had a 6-month cumulative incidence of VTE of almost 10% [22]. Therefore, it has been proposed that a score of $\geq$2 may define patients with cancer at high risk of VTE [22,42], and was further used to define the study population in the two RCTs evaluating the use of prophylactic direct oral anticoagulants (DOACs) as risk-stratified primary thromboprophylaxis in patients with cancer (AVERT and Cassini trials) [5,6].

Various modifications to the Khorana score, such as the Vienna CATS, PROTECHT CONKO, and ONKOTEV scores, have been proposed to improve the discriminatory performance [22,23,40,41]. These scores include some or all the parameters of the Khorana score, with the addition of other parameters such as biomarkers (e.g., D-dimer, soluble P-selectin) and clinical factors (e.g., platinum or gemcitabine chemotherapy, performance status) [22,23,40,41] (Table 1). Most of these newer scores have not been extensively externally validated, and thus far have limited clinical utility [5,6,45-47].

There are also novel risk assessment models that have been developed aiming to better predict the overall risk of VTE in patients with cancer [24,48-50] (Table 2). The COMPASS-CAT score, prospectively developed in a cohort of patients with breast, ovarian, lung and colorectal cancers, includes clinical characteristics, comorbidities and treatment parameters that are different than those in the Khorana score [24]. On the other hand, the CATSCORE by Pabinger et al[48] is a nomogram that uses tumor site and D-dimer to estimate an individual's risk of VTE, whereas the Tic-ONCO and ONCOTHROMB risk assessment models incorporate clinical variables and genetic variants (single nucleotide polymorphisms (SNP) alleles) to determine the risk of VTE [48-50]. There have also been efforts to develop cancer-specific risk assessment tools such as ROADMAP-CAT for lung adenocarcinoma, THROMBOGYN for gynecologic cancer, THROLY for lymphoma, and more, however, none had been sufficiently validated nor used in clinical practice [24,44,51-53]. A biomarker-based risk assessment model that uses fibrinogen and D-dimer levels has also recently been evaluated for targeted thromboprophylaxis in the TARGET-TP trial. In this RCT (N = 328), patients with lung or gastrointestinal cancer deemed at high risk of VTE (by fibrinogen and D-dimer levels pre-treatment or at one month after treatment) were randomized to thromboprophylaxis with enoxaparin versus no thromboprophylaxis [54]. The risk stratification at 1-month time post-treatment start is a novel and innovative use of a risk assessment model as it has the potential to capture the prothrombotic effects of systemic therapies [54]. Although D-dimer is a commonly available biomarker and is included in various risk prediction models as mentioned above, currently it is not routinely assessed in clinical practice to guide decisions on primary thromboprophylaxis in patients with cancer. This may be due to many factors, including the need for more external validation of risk prediction models as well as the lack of a unified measurement methodology in D-dimer, which could lead to confusion.

There remain areas for improvement and knowledge gaps in risk stratification for CAT. A significant limitation of the most current risk assessment models is their reliance on a single measurement at a specific time point (commonly upon cancer diagnosis prior to start of anticancer therapies), failing to account for the dynamic nature of the patient- and treatment-related VTE risk factors over the course of a patient's cancer journey [46,47]. Another issue with the current risk assessment models is that many VTE events still occur in patients classified as low or intermediate risk, indicating that the predictive power is far from perfect, and other predictive markers may need to be elucidated [55]. Finally, it is also important to have tools that can help better understand the risk of bleeding in patients with cancer at the same time, as the risk of bleeding is a major concern associated with thromboprophylaxis and the risk-benefit balance is critical in the decision-making process [43].

Primary thromboprophylaxis in ambulatory patients with cancer

While initial RCTs including the PROTECHT and SAVE-ONCO showed that thromboprophylaxis with LMWH significantly reduced the VTE risk in unselected cancer patients across a spectrum of solid tumors, the absolute risk reduction was thought to be modest and these results did not translate into routine clinical practice. Subsequent trials aimed to target high-risk patients by using risk prediction models, mainly the Khorana score, to improve risk benefit ratio. The first was the PHACS trial to evaluate the benefit of outpatient thromboprophylaxis with dalteparin in high-risk patients with cancer (i.e., Khorana score of $\geq$3) [56]. Although the PHACS trial did not reach the accrual target, 98 patients were randomized (50 to dalteparin and 48 to observation). Dalteparin was associated with a trend of lower risk of VTE (although not statistically significant), 12% vs 21% (dalteparin vs observation), with hazard ratio (HR) of 0.69 (95% CI 0.23–1.89) [56]. The primary safety outcome of clinically-relevant bleeding events occurred in 7 patients in the dalteparin arm

compared with 1 in the observation arm, for an HR of 7.02 (95% CI 1.24–131.6) [56]. Major bleeding, however, only occurred in one patient in each arm [56]. An individual patient-level metanalysis of RCTs similarly found that LMWH decreased the risk of VTE by 64% compared to placebo or observations (OR 0.36; 95% CI 0.22–0.58) in patients with Khorana score ≥3 [57].

More recently, two RCTs, CASSINI and AVERT, set out to evaluate low dose DOACs, rivaroxaban and apixaban, respectively, as primary thromboprophylaxis in ambulatory patients with cancer and intermediate-to-high risk of VTE (defined by Khorana score ≥2) [5,6].

The CASSINI trial was an international, double-blind, placebo-controlled, randomized, superiority trial [6]. Patients underwent lower-extremity compressive sonography to screen for preexisting deep vein thrombosis (DVT) prior to randomization. Participants without DVT were randomized to rivaroxaban 10 mg daily or placebo for up to 6 months. Repeat compressive ultrasonography was planned every eight weeks. The primary efficacy outcome was a composite of incidental or symptomatic proximal lower-extremity DVT or PE, symptomatic upper-extremity DVT or lower-extremity distal DVT, or VTE-related death during the six-month follow-up period. The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). A total of 49 (4.5%) patients were diagnosed with a DVT at the first screening ultrasound and excluded from randomization. The intention-to-treat analysis included 841 patients (420 in the rivaroxaban group and 421 in the placebo group). Overall, 32.6% of patients had pancreatic cancer, 20.9% had gastric or gastroesophageal junction cancer, and 15.9% had lung cancer. In the intention-to-treat analysis, the primary efficacy outcome occurred in 6.0% of the patients in the rivaroxaban group, non-significantly lower compared with 8.8% in the placebo group (HR 0.66; 95% CI 0.40–1.09; $P = 0.10$). In a pre-specified on-treatment analysis (only

including outcomes occurring on or until 2 days after study drugs), the primary efficacy outcome occurred in 2.6% of patients in the rivaroxaban group, significantly lower than the 6.4% in the placebo group (HR 0.40; 95% CI 0.20–0.80). Major bleeding occurred in 2.0% of patients receiving rivaroxaban and 1.0% of the patients receiving placebo (HR 1.96; 95% CI 0.59–6.49). Clinically relevant non-major bleeding (CRNMB) was ascertained in 2.7% of patients receiving rivaroxaban compared with 2.0% of those receiving placebo (HR 1.34; 95% CI 0.54–3.32) [6].

The AVERT trial was a double-blind, placebo-controlled randomized trial comparing the use of apixaban 2.5 mg twice daily to placebo for thromboprophylaxis of intermediate-high-risk ambulatory cancer patients receiving chemotherapy [5]. Eligible patients were randomized in a 1:1 ratio to receive apixaban or placebo. Unlike the CASSINI trial, no screening ultrasonography was done at baseline or throughout the six month follow up period. The primary efficacy outcome was a composite of symptomatic or incidental proximal upper-extremity or lower-extremity DVT, symptomatic or incidental PE, or PE-related death. The main safety outcome was major bleeding by ISTH criteria. A total of 574 patients were randomized, and 563 were included in the modified intention-to-treat analysis. The most common cancer types were gynecological (25.8%), lymphoma (25.3%), and pancreatic (13.6%). The primary efficacy outcome occurred in 4.2% of the patients in the apixaban group, significantly lower than 10.2% of patients in the placebo group (HR 0.41; 95% CI 0.26–0.65; $P = 0.001$). Major bleeding occurred in 3.5% of the patients receiving apixaban and 1.8% of patients receiving placebo (HR 2.00; 95% CI 1.01-3.95; $P = 0.046$). CRNMB was noted in 7.3% of the patients receiving apixaban and 5.5% of those receiving placebo (HR 1.28; 95% CI 0.89–1.84). In the secondary on-treatment analysis, the primary efficacy outcome occurred in 1.0% of the patients in the apixaban group compared with 7.3% in the

placebo group (HR 0.14; 95% CI 0.05–0.42), and major bleeding occurred in 2.1% in the apixaban group and 1.1% in the placebo group (HR 1.89; 95% CI 0.39–9.24) [5].

When combining the results of the AVERT and CASSINI trials in an intention-to-treat analysis, the relative risk of VTE at six months was 0.56 (95% CI 0.38–0.83) (DOAC vs placebo), with the number needed to treat of 24 [58]. The relative risk of major bleeding was 1.96 (95% CI 0.88–4.33) for a number needed to harm of 77 [58]. Furthermore, the risk of death from any cause was unchanged with the use of thromboprophylaxis (RR 0.92; 95% CI 0.73–1.16) [58]. While combining the results of the AVERT and CASSINI trials offers a better understanding of the VTE burden and efficacy of thromboprophylaxis in patients with cancer and Khorana score $\geq$2, there are important distinctions between the two studies. Key differences include: patients with primary brain cancer or cerebral metastases were excluded from CASSINI but not AVERT; CASSINI included a large proportion of pancreatic and gastric or gastroesophageal cancer patients whereas AVERT had more hematological and gynecological cancer patients; CASSINI study focused recruitment of patients with locally advanced or metastatic cancer, whereas the AVERT study included all patients with newly diagnosed or progressive cancer starting chemotherapy; CASSINI required all patients to undergo a screening ultrasound before randomization, while no screening ultrasounds were employed in the AVERT trial [5,6,8]. Despite the differences in the trial designs and patient populations included in the AVERT and CASSINI trials, international guidelines and guidance statements have been updated to incorporate these results as supporting evidence for consideration of primary thromboprophylaxis in patients with cancer at intermediate-to-high risk of VTE [34-39].

Most recently, the above-mentioned TARGET-TP trial also showed that thromboprophylaxis with enoxaparin significantly reduced the risk of CAT in those identified as high risk based on a different risk assessment approach using fibrinogen and D-dimer

levels (enoxaparin vs placebo: 8% vs 23%, HR 0.31; 95% CI 0.15–0.70, *P* = 0.005, NNT = 6.7). There was no increased risk of major bleeding associated with enoxaparin in this trial (1% vs 2%, *P* = 0.88) [54].

Multiple myeloma Patients with multiple myeloma (MM) are at high risk of developing VTE due to unique disease-related complications and treatment-related toxicities, especially from immunomodulatory drugs (IMiDs) [59]. Patients with MM were under-represented in the original Khorana cohort, and thus many MM-specific risk factors for VTE were not included in the Khorana score. Furthermore, the Khorana score has been shown to have poor prediction performance for the risk of VTE in patients with MM [60]. Four myeloma-specific risk assessment models have been proposed to predict the risk of VTE (Figure 2). The first model was based on expert consensus proposed by the International Myeloma Working Group (IMWG) and later adopted by the National Comprehensive Cancer Network (NCCN) [61,62]. Despite the incorporation of the IMWG/NCCN thromboprophylaxis guidelines, the cumulative incidence of VTE in the first year after MM diagnosis remained substantial and attempts at externally validating the IMWG/NCCN risk stratification model were unsuccessful [63,64]. The SAVED and IMPEDE-VTE risk prediction models were then specifically derived and externally validated to estimate the risk of VTE in patients with newly diagnosed MM [63,65] (Figure 2). Most recently, the PRISM score was derived, which included patient-, disease-, and treatment-specific factors in the context of modern antimyeloma therapy [66]. External prospective validation in larger population is still needed before these scores can be incorporated into clinical practice [66]. Overall, guidelines recommend that thromboprophylaxis should be considered in patients with MM assessed at high risk for VTE, especially newly diagnosed patients receiving ImiD-based combination therapies [67].

Factors to consider when initiating primary thromboprophylaxis in ambulatory patients with cancer

While primary thromboprophylaxis is suggested to be considered in patients with cancer at intermediate-to-high risk of VTE, the decision to initiate primary thromboprophylaxis needs to incorporate evaluation of the risk of bleeding, potential drug-drug interactions (DDIs) and organ functions. It is also imperative to discuss patients' preferences and potential costs associated with primary thromboprophylaxis.

Bleeding risk Patients with cancer receiving anticoagulation therapy have 2- to 3-fold increased risk of bleeding events compared to patients without cancer [68,69]. In a systematic review and meta-analysis including ambulatory patients with cancer and Khorana score ≥2 receiving primary thromboprophylaxis with either LMWH or DOACs, the risk of major bleeding with thromboprophylaxis was not significantly increased. However, a subgroup analysis restricting to patients receiving thromboprophylaxis with a DOACs (AVERT and CASSINI trials), a relatively high RR of major bleeding of 1.96 (95% CI, 0.69-5.50) [70]. There is no clear consensus on the best risk assessment model that reliably identify patients with cancer who are at high risk of bleeding. Hence, bleeding risk is still often determined based on clinical judgment [71].

Factors that increase the risk of bleeding include history of bleeding events, recent surgery, bleeding from unresected primary tumor (i.e., gastrointestinal tract, genitourinary tract and gynecological malignancies, intracranial malignancy), metastatic disease, thrombocytopenia, anemia, liver and renal dysfunction, as well as certain anticancer therapies (e.g. anti-angiogenesis treatments, tyrosine kinase inhibitors) [68,72,73]. A secondary analysis of the AVERT trial evaluated specific risk factors associated with an increased risk of bleeding events in patients with cancer receiving apixaban thromboprophylaxis [74]. Notably, apixaban thromboprophylaxis was associated with an increased risk of combined major

bleeding and clinically relevant non-major bleeding in patients with age ≥65, weight <90 kg, cancer types other than gastrointestinal / genitourinary / gynecological, and a Khorana score of 2 [74]. Surprisingly, renal insufficiency and antiplatelet use were not correlated with bleeding events in this cohort [74]. While this analysis provides interesting insights, these identified risk factors are not absolute contraindications to primary thromboprophylaxis with apixaban. Evaluating bleeding risks in cancer patients necessitates individualized clinical judgment, and reassessment of this risk throughout the patient's cancer journey is imperative.

<2>Drug-Drug interactions When considering the use of primary thromboprophylaxis in patients with cancer, it is important to consider the risk of DDIs between the anticoagulation agent of choice (LMWH, DOAC) and anticancer treatments, supportive medications, as well as medications used for comorbid conditions [75,76]. Apixaban and rivaroxaban are substrates of P-glycoprotein (P-gp) and Cytochrome (CYP) 3A4, so other drugs that significantly affect P-gp or CYP3A4 metabolism could have the potential to affect the safety or efficacy of DOACs. Previous reviews have extensively summarized many of the common anticancer therapies that affect the P-gp or CYP 3A4 pathways and are a good resource for clinicians when evaluating for potential DDIs [77-79]. LMWH is not metabolized through the CYP 3A4 or P-gp pathways and is therefore the recommended anticoagulant if there DDI is a concern [76]. However, recent studies showed potentially important pharmacodynamic interactions between LMWH and vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) suggesting that an increased risk of bleeding may still need to be considered [76]. As anticancer therapies continue to rapidly evolve, more potential DDIs could affect the efficacy and safety of anticoagulants. It is also worth noting that many DDIs are theoretical concerns, and more data are needed for their clinical relevance. Clinicians should routinely evaluate potential DDIs with anticoagulation and other medications by using

existing evidence and consulting resources such as product labelling, large pharmacology databases with drug interaction function, and/or consulting with the local pharmacists [76].

Organ function Renal and liver dysfunction are common in patients with cancer. As both LMWH and DOACs rely on the kidney and/or liver for metabolism and / or elimination, it is important to consider organ function when evaluating for primary thromboprophylaxis [80]. Renal and/or liver dysfunction can lead to drug accumulation, which consequently leads to higher plasma concentration of an anticoagulant and an increased risk of bleeding [80]. In existing trials evaluating primary thromboprophylaxis patients with cancer, individuals with a creatinine clearance <30 mL/min or with significant liver dysfunction were excluded and thus the results may not be applicable to patients with significant renal and/or hepatic impairment [5,6,31,32].

Central venous catheter Central venous catheters (CVCs) are frequently placed to facilitate the administration of chemotherapy, blood products, parenteral nutrition, and other supportive therapies in patients with cancer. The presence of a CVC is also an important risk factor for VTE in patients with cancer [81]. Even patients with lower-risk tumor types (e.g., breast cancer, colorectal cancer) have been reported to have higher risk of VTE because of the CVC [81,82]. In a recent systematic review and meta-analysis, primary thromboprophylaxis is associated with a favorable risk-benefit ratio in patients with cancer and a CVC [83]. Similar findings were also reported in a subgroup analysis of the AVERT trial [84]. These results suggest that there may be a role for primary thromboprophylaxis in patients with cancer and a CVC, but it requires further investigation and has not been recommended by major clinical practice guidelines. [35,38,39] A large multicenter RCT comparing primary thromboprophylaxis with rivaroxaban 10 mg once daily to placebo in patients with cancer and a CVC is currently underway (NCT05029063) [82].

Duration of primary thromboprophylaxis

The optimal duration of primary thromboprophylaxis in ambulatory patients with cancer receiving chemotherapy is not well-established. In both the AVERT and the CASSINI trials, a follow-up period of 6 months was chosen as it corresponds to the time period of the highest risk of VTE [5,6,85]. Six months is also the approximate duration of many chemotherapy regimens. Based on current evidence, if primary thromboprophylaxis is initiated, it should be continued for at least six months as per the AVERT and CASSINI trials. It is important to remember that the risk-benefit of primary thromboprophylaxis must be regularly reassessed to determine the appropriateness of the ongoing anticoagulant use. Whether thromboprophylaxis should be continued beyond 6 months can be determined based on a patient's ongoing risk of VTE, risk of bleeding, cancer status, as well as patient's preference.

Conclusions Cancer-associated thrombosis is a common complication among ambulatory patients receiving chemotherapy. Many risk factors including cancer type and stage, patient characteristics, and anticancer treatments influence the risk of CAT. Primary thromboprophylaxis with LMWH or DOACs is an effective and relatively safe option to prevent CAT and could be considered in patients with cancer who are at intermediate-to-high risk of VTE, after a careful review of the patient's bleeding risk, organ function, and potential DDIs.

Article information

Acknowledgments M. Carrier is the recipient of Tier 1 Research Chair from the University of Ottawa in Cancer and Thrombosis.

Funding None.

Conflict of interest M. Carrier reports grants from BMS, Leo Pharma and Pfizer, personal fees from BMS, Leo Pharma, Bayer, Pfizer, Servier and Sanofi. The other authors report no conflict of interest.

How to cite Harrigan AM, Carrier M, Wang T-F. Primary prevention of venous thromboembolism in ambulatory cancer patients: recent advances and practical implications. Pol Arch Intern Med. 2024; XX: 16739. doi:10.20452/pamw.16739.

References

1 Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood. 2021; 137: 1959-1969.

2 Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. Thromb Haemost. 2017; 117: 219-230.

3 Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013; 122: 1712-1723.

4 Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007; 5: 632-634.

5 Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Eng J Med. 2019; 380: 711-719.

6 Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Eng J Med. 2019; 380: 720-728.

7 Steiner D, Ay C. Risk assessment and primary prevention of VTE in patients with cancer: Advances, challenges, and evidence gaps. Best Pract Res Clin Haematol. 2022; 35: 101347.
8 Khorana AA, Cohen AT, Carrier M, et al. Prevention of venous thromboembolism in ambulatory patients with cancer. ESMO Open. 2020; 5: e000948.
9 Ashrani AA, Gullerud RE, Petterson TM, et al. Risk factors for incident venous thromboembolism in active cancer patients: a population based case-control study. Thromb Res. 2016; 139: 29.
10 Roy DC, Wang TF, Carrier M, et al. Thrombophilia gene mutations predict venous thromboembolism in ambulatory cancer patients receiving chemotherapy. J Thromb Haemost. 2023; 21: 3184-3192.
11 Englisch C, Moik F, Nopp S, et al. ABO blood group type and risk of venous thromboembolism in patients with cancer. Blood Adv. 2022; 6: 6274.
12 Dickmann B, Ahlbrecht J, Ay C, et al. Regional lymph node metastases are a strong risk factor for venous thromboembolism: results from the Vienna Cancer and Thrombosis Study. Haematologica. 2013; 98: 1309.
13 Ahlbrecht J, Dickmann B, Ay C, et al. Tumor grade is associated with venous thromboembolism in patients with cancer: results from the vienna cancer and thrombosis study. 2012; 30: 3870-3875.
14 Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000; 160: 809-815.
15 Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA. 2008; 300: 2277-2285.

16 Seng S, Liu Z, Chiu SK, et al. Risk of venous thromboembolism in patients with cancer treated with Cisplatin: a systematic review and meta-analysis. J Clin Oncol. 2012; 30: 4416-4426.

17 Wang TF, Carrier M. Immune checkpoint inhibitors-associated thrombosis: incidence, risk factors and management. Current Oncology. 2023; 30: 3032-3046.

18 Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. Nat Rev Dis Primers. 2022; 8: 1-18.

19 Hisada Y, Mackman N. Mechanisms of cancer-associated thrombosis. Res Pract Thromb Haemost. 2023; 7.

20 Rosell A, Martinod K, Mackman N, Thålin C. Neutrophil extracellular traps and cancer-associated thrombosis. Thromb Res. 2022; 213: S35-S41.

21 Khorana A, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008; 111: 4902-4907.

22 Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. Blood. 2010; 116: 5377-5382.

23 Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med. 2012; 7: 291-292.

24 Gerotziafas GT, Taher A, Abdel-Razeq H, et al. A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS–Cancer-Associated Thrombosis Study. Oncologist. 2017; 22: 1222.

25 Ay C, Simanek R, Vormittag R, et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). Blood. 2008; 112: 2703-2708.

26 Ay C, Vormittag R, Dunkler D, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: Results from the Vienna Cancer and Thrombosis Study. J Clin Oncol. 2009; 27: 4124-4129.
27 Vormittag R, Simanek R, Ay C, et al. High Factor VIII Levels Independently Predict Venous Thromboembolism in Cancer Patients. Arterioscler Thromb Vasc Biol. 2009; 29: 2176-2181.
28 Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: Outcomes from the CONKO-004 trial. J Clin Oncol. 2015; 33: 2028-2034.
29 Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer. 2012; 48: 1283-1292.
30 Haas SK, Freund M, Heigener D, et al. Low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer or stage III/IV lung cancer. Clin Appl Thromb Hemost. 2012; 18: 159-165.
31 Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol. 2009; 10: 943-949.
32 Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Eng J Med. 2012; 366: 601-609.
33 Rutjes AWS, Porreca E, Candeloro M, et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev. 2020; 12: CD008500.

34 Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. Lancet Oncol. 2022; 23: e334-e347.
35 Streiff MB, Holmstrom B, Angelini D, et al. Cancer-associated venous thromboembolic disease, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19: 1181-1201.
36 Wang TF, Zwicker JI, Ay C, et al. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: Guidance from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2019; 17: 1772-1778.
37 Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline. Ann Oncol. 2023; 34: 452-467.
38 Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update. J Clin Oncol. 2023; 41: 3063-3071.
39 Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021; 5: 927-974.
40 Pelzer U, Sinn M, Stieler J, Riess H. Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy?. Dtsch Med Wochenschr. 2013; 138: 2084-2088. [in German]
41 Cella CA, Di Minno G, Carlomagno C, et al. Preventing Venous Thromboembolism in Ambulatory Cancer Patients: The ONKOTEV Study. Oncologist. 2017; 22: 601-608.
42 Mulder FI, Candeloro M, Kamphuisen PW, et al. The khorana score for prediction of venous thromboembolism in cancer patients: A systematic review and meta-analysis. Haematologica. 2019; 104: 1277-1287.

43 Khorana AA, Francis CW. Risk prediction of cancer-associated thrombosis: Appraising the first decade and developing the future. Thromb Res. 2018; 164: S70-S76.
44 Moik F, Englisch C, Pabinger I, Ay C. Risk assessment models of cancer-associated thrombosis - Potentials and perspectives. Thrombosis Update. 2021; 5: 100075.
45 Khorana AA, DeSancho MT, Liebman H, et al. Prediction and Prevention of Cancer-Associated Thromboembolism. Oncologist. 2021; 26: e2-e7.
46 van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica. 2017; 102: 1494.
47 Di Nisio M, van Es N, Rotunno L, et al. Long-term performance of risk scores for venous thromboembolism in ambulatory cancer patients. J Thromb Thrombolysis. 2019; 48: 125-133.
48 Pabinger I, van Es N, Heinze G, et al. Development and validation of a clinical prediction model for cancer-associated venous thromboembolism in two independent prospective cohorts. Lancet Haematol. 2018; 5: e289.
49 Martín AJM, Ortega I, Font C, et al. Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. Br J Cancer. 2018; 118: 1056.
50 Muñoz A, Ay C, Grilz E, et al. A clinical-genetic risk score for predicting cancer-associated venous thromboembolism: a development and validation study involving two independent prospective cohorts. J Clin Oncol. 2023; 41: 2911.
51 Antic D, Milic N, Nikolovski S, et al. Development and validation of multivariable predictive model for thromboembolic events in lymphoma patients. Am J Hematol. 2016; 91: 1014-1019.

52 Syrigos K, Grapsa D, Sangare R, et al. Prospective assessment of clinical risk factors and biomarkers of hypercoagulability for the identification of patients with lung adenocarcinoma at risk for cancer-associated thrombosis: the observational ROADMAP-CAT Study. Oncologist. 2018; 23: 1372-1381.
53 Norris LA, Ward MP, O'Toole SA, et al. A risk score for prediction of venous thromboembolism in gynecologic cancer: the Thrombogyn score. Res Pract Thromb Haemost. 2020; 4: 848.
54 Alexander M, Harris S, Underhill C, et al. Risk-Directed Ambulatory Thromboprophylaxis in Lung and Gastrointestinal Cancers: The TARGET-TP Randomized Clinical Trial. JAMA Oncol. 2023; 9: 1536-1545.
55 Moik F, Ay C, Pabinger I. Risk prediction for cancer-associated thrombosis in ambulatory patients with cancer: past, present and future. Thromb Res. 2020; 191: S3-S11.
56 Khorana AA, Francis CW, Kuderer NM, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: A randomized trial. Thromb Res. 2017; 151: 89-95.
57 van Es N, Ventresca M, Di Nisio M, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: An individual patient data meta-analysis. Journal of Thrombosis and Haemostasis. 2020; 18: 1940-1951.
58 Agnelli G. Direct oral anticoagulants for thromboprophylaxis in ambulatory patients with cancer. N Eng J Med. 2019; 380: 781-783.
59 Chakraborty R, Majhail NS. Treatment and disease-related complications in multiple myeloma: Implications for survivorship. Am J Hematol. 2020; 95: 672-690.
60 Sanfilippo KM, Carson KR, Wang TF, et al. Evaluation of the Khorana score for prediction of venous thromboembolism in patients with multiple myeloma. Res Pract Thromb Haemost. 2022; 6: e12634.

61 Palumbo A, Rajkumar S V., Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008 22:2. 2007; 22: 414-423.
62 Streiff MB, Holmstrom B, Angelini D, et al. NCCN guidelines insights: cancer-associated venous thromboembolic disease, Version 2.2018. J Natl Compr Canc Netw. 2018; 16: 1289-1303.
63 Li A, Wu Q, Luo S, et al. Derivation and validation of a risk assessment model for immunomodulatory drug-associated thrombosis among patients with multiple myeloma. J Natl Compr Canc Netw. 2019; 17: 840-847.
64 Chakraborty R, Bin Riaz I, Malik SU, et al. Venous thromboembolism risk with contemporary lenalidomide-based regimens despite thromboprophylaxis in multiple myeloma: a systematic review and meta-analysis. Cancer. 2020; 126: 1640-1650.
65 Sanfilippo KM, Luo S, Wang TF, et al. Predicting venous thromboembolism in multiple myeloma: development and validation of the IMPEDE VTE Score. Am J Hematol. 2019; 94: 1176.
66 Chakraborty R, Rybicki L, Wei W, et al. Abnormal metaphase cytogenetics predicts venous thromboembolism in myeloma: derivation and validation of the PRISM score. Blood. 2022; 140: 2443-2450.
67 Callander NS, Baljevic M, Adekola K, et al. NCCN Guidelines® insights: multiple myeloma, version 3.2022: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2022; 20: 8-19.
68 Angelini DE, Radivoyevitch T, McCrae KR, Khorana AA. Bleeding incidence and risk factors among cancer patients treated with anticoagulation. Am J Hematol. 2019; 94: 780-785.
69 Trujillo-Santos J, Nieto JA, Ruíz-Gamietea Á, et al. Bleeding complications associated with anticoagulant therapy in patients with cancer. Thromb Res. 2010; 125 Suppl 2: S58-S61.

70 Bosch FTM, Mulder FI, Willem Kamphuisen P, et al. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. Blood Adv. 2020; 4: 5215-5225.
71 Sanfilippo KM, Yan Y, Carrier M, Gage BF. Discriminating risk of anticoagulant-related bleeding in ambulatory cancer patients on thromboprophylaxis. Blood. 2023; 142: 567.
72 Frere C, Font C, Esposito F, et al. Incidence, risk factors, and management of bleeding in patients receiving anticoagulants for the treatment of cancer-associated thrombosis. Supportive Care in Cancer. 2022; 30: 2919-2931.
73 Vedovati MC, Giustozzi M, Munoz A, et al. Risk factors for recurrence and major bleeding in patients with cancer-associated venous thromboembolism. Eur J Intern Med. 2023; 112: 29-36.
74 Castellucci LA, Carrier M, Mallick R, Wells PS. Bleeding in the prevention of cancer-associated venous thromboembolism: secondary analysis of the AVERT Study. Research Practice Thrombosis Haemostasis. 2019; 3: 719-719.
75 Ng HK, Rogala BG, Ades S, et al. Prospective evaluation of drug-drug interactions in ambulatory cancer patients initiated on prophylactic anticoagulation. J Oncol Pharm Pract. 2020; 26: 1637-1642.
76 Wang TF. Drug-drug interactions: Implications for anticoagulation, with focus in patients with cancer. Thromb Res. 2022; 213 Suppl 1: S66-S71.
77 Wang TF, Baumann Kreuziger L, Leader A, et al. Characteristics and outcomes of patients on concurrent direct oral anticoagulants and targeted anticancer therapies—TacDOAC registry: Communication from the ISTH SSC Subcommittee on Hemostasis and Malignancy. J Thromb Haemost. 2021; 19: 2068-2081.
78 Kraaijpoel N, Carrier M. How I treat cancer-associated venous thromboembolism. Blood. 2019; 133: 291-298.

79 Short NJ, Connors JM. New oral anticoagulants and the cancer patient. Oncologist. 2014; 19: 82-93.
80 Ribic C, Crowther M. Thrombosis and anticoagulation in the setting of renal or liver disease. Hematology. 2016; 2016: 188-195.
81 Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol. 2003; 21: 3665-3675.
82 Ikesaka R, Siegal D, Mallick R, et al. Thromboprophylaxis with rivaroxaban in patients with malignancy and central venous lines (TRIM-Line): A two-center open-label pilot randomized controlled trial. Res Pract Thromb Haemost. 2021; 5.
83 Li A, Brandt W, Brown C, et al. Efficacy and safety of primary thromboprophylaxis for the prevention of venous thromboembolism in patients with cancer and a central venous catheter: A systematic review and meta-analysis. Thromb Res. 2021; 208: 58-65.
84 Brandt W, Brown C, Wang TF, et al. Efficacy and safety of apixaban for primary prevention of thromboembolism in patients with cancer and a central venous catheter: A subgroup analysis of the AVERT Trial. Thromb Res. 2022; 216: 8-10.
85 Blix K, Gran OV, Severinsen MT, et al. Impact of time since diagnosis and mortality rate on cancer-associated venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) cohort. J Thromb Haemost. 2018; 16: 1327-1335.

Table 1 Overview of published risk assessment models for cancer-associated thrombosis (adapted from [55])					
	Khorana (2008) [21]	**Vienna CATS (2010)** [22]	**PROTECHT (2012)** [23]	**CONKO (2013)** [40]	**ONKOTEV (2017)** [41]
Parameter					
Very high-risk tumors (pancreatic, gastric)	+ 2	+ 2	+ 2	+ 2	Khorana score >2
High risk tumors (lung, gynecological, lymphoma, bladder, testicular)	+ 1	+ 1	+ 1	+ 1	
Pre-chemotherapy hemoglobin <10 g/dL	+ 1	+ 1	+ 1	+ 1	
Pre-chemotherapy leukocyte count $\geq$11 x 10^9/L	+ 1	+ 1	+ 1	+ 1	
Pre-chemotherapy platelet count $\geq$350 x 10^9/L	+ 1	+ 1	+ 1	+ 1	
BMI $\geq$35 kg/m^2	+ 1	+ 1	+ 1	-	
D-dimer >1.44 ug/L	-	+ 1	-	-	-

Soluble P-selectin >53.1 ng/L	-	+ 1	-	-	-
Gemcitabine chemotherapy	-	-	+ 1	-	-
Platinum-based chemotherapy	-	-	+ 1	-	-
ECOG performance status ≥2	-	-	-	+ 1	-
Metastatic disease	-	-	-	-	+ 1
Previous VTE	-	-	-	-	+ 1
Vascular/lymphatic macroscopic compression	-	-	-	-	+ 1
Proposed cut-off					
	≥2/ ≥3	**≥3**	**≥3**	**≥3**	NR
External validation[a]					
	+++	**ND**	**+**	**+**	+

a The + signs refer to whether an external validation was done or not, +++ signifies several external validations were done

Abbreviations: BMI, body mass index, ND not done, NR, not reported

Table 2 Overview of novel risk assessment models for cancer-associated thrombosis				
	COMPASS-CAT (2017) [24]	**Pabinger et al. (2018)** [48]	**TIC-Onco (2018)** [49]	**ONCOTHROMB (2023)** [50]
Parameter				
Comments	Only for use in breast, colorectal, lung, and ovarian cancer Clinical parameters and treatment parameters different from Khorana score	Nomogram	Adds genetic risk factors	Adds genetic risk factors
Personal history of VTE	+ 1	-	-	-
Cardiovascular risk factor[a]	+ 5	-	-	-
Recent hospitalization for acute medical illness	+ 5	-	-	-

BMI >25 kg/m^2	-	-	X	X
Family history of VTE	-	-	X	-
Tumour type	-	X	X	X
Advanced cancer stage	+ 2	-	X	X
Time since cancer diagnosis $\leq$6 months	+ 4	-	-	-
Anti-hormonal therapy in hormone positive breast cancer or anthracycline chemotherapy	+ 6	-	-	-
Central venous catheter use	+ 3	-	-	-
Platelet count $\geq$350 x10^9/L	+ 2	-	-	-
D-Dimer (continuous)	-	X	-	-
Genetic SNPs	-	-	X	X
Proposed cut-off				

	≥ 7	Personalized risk prediction	Different cut-offs based on sensitivity	Youden J statistic as the point that maximizes the Youden index
External validation				
	+	+	+	-

a At least two of: personal history of peripheral artery disease, ischaemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes or obesity

Abbreviations: BMI, body mass index, SNPs, single nucleotide polymorphisms, VTE, venous thromboembolism

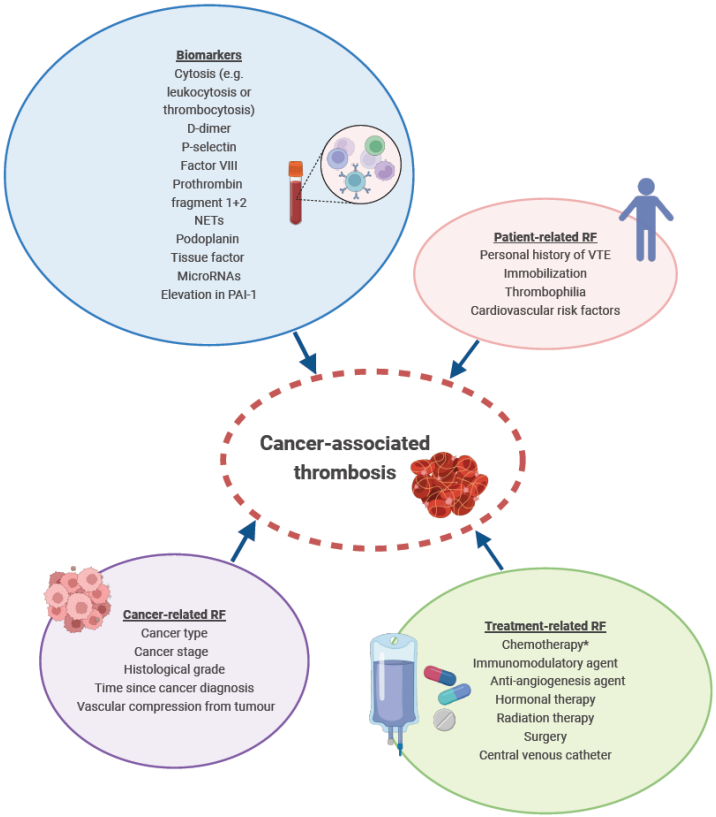

Figure 1 Risk factors for development of cancer-associated thrombosis (generated with BioRender.com)

Abbreviations: NETs, neutrophil extracellular traps, PAI-1, plasminogen activator inhibitor-1, VTE, venous thromboembolism

*High risk chemotherapy includes platinum-based therapy, anthracycline-containing therapy

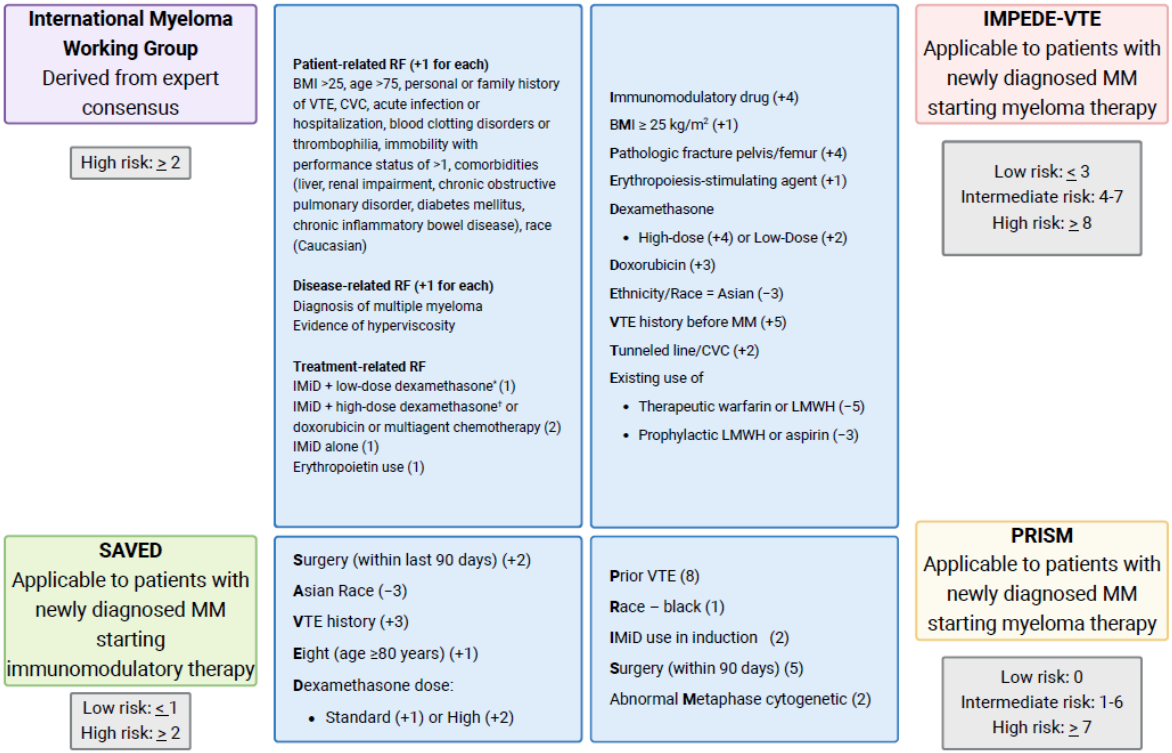

Figure 2 Overview of risk assessment models for venous thromboembolism in newly diagnosed multiple myeloma (generated with BioRender.com)

Abbreviations: BMI, body mass index, CVC, central venous catheter, IMiD, immunomodulatory agent, LMWH, low molecular weight heparin, MM, multiple myeloma, mo, month, VTE, venous thromboembolism

*Low dose dexamethasone: (<480 mg/mo)

†High dose dexamethasone (>480 mg/mo)