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Prediction and Prevention of Cancer-Associated Thromboembolism

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Abstract

Venous and arterial thromboembolism are prevalent, highly burdensome, and associated with risk of worse outcomes for patients with cancer. Risk for venous thromboembolism (VTE) varies widely across specific cancer subpopulations. The ability to predict risk of cancer-associated VTE is critical because an optimal thromboprophylaxis strategy is best achieved by targeting high-risk patients with cancer and avoiding prophylaxis in patients with cancer at low risk for VTE. A validated risk tool for solid tumors has been available for a decade. Newer tools have focused on specific populations, such as patients with multiple myeloma. Emerging studies continue to optimize risk prediction approaches in patients with cancer. Recent randomized trials have specifically addressed risk-adapted thromboprophylaxis using direct oral anticoagulants, and revised guidelines have included these new data to formulate recommendations for outpatient thromboprophylaxis. Implementation science approaches to enhance use of outpatient prophylaxis in the context of these guideline changes are under way. However, major knowledge gaps remain, including a lack of data for inpatient thromboprophylaxis in the cancer setting and a lack of formal tools for identifying risk of bleeding. This review describes optimal approaches to risk prediction and patient selection for primary pharmacologic thromboprophylaxis of cancer-associated VTE, addresses barriers to implementing these practices, and highlights strategies to overcome them. ***The Oncologist*** 2021;26:e2–e7

Implications for Practice: Risk for venous thromboembolism (VTE) varies widely among patients with cancer. Individual risk can be determined using validated approaches. Inpatient and postsurgical thromboprophylaxis is more widely accepted. However, most patients with cancer develop VTE in the outpatient setting. Recent randomized trials have demonstrated benefit to risk-adapted outpatient thromboprophylaxis. High-risk patients may therefore be considered for outpatient thromboprophylaxis as recommended by recently updated guidelines. System-wide implementation approaches are necessary to improve compliance with prophylaxis.

Introduction

The association between cancer and venous thromboembolism (VTE, comprising deep vein thrombosis [DVT] and pulmonary embolism [PE]) and arterial thromboembolism (ATE, including myocardial infarction, stroke, and peripheral arterial embolism) has long been known [1]. The risk of VTE has persisted with newer anticancer therapies and appears to increase with the use of specific anticancer drugs, including antiangiogenic agents, multitargeted tyrosine kinase inhibitors, immunomodulatory drug combinations, and potentially even immunotherapy regimens [2, 3]. VTE and ATE are both

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consequential for patients with cancer—directly, by increasing short-term mortality, hospitalization, and emergency room visits, and indirectly, given the association with worse outcomes, including decreased survival and poorer quality of life [4, 5].

Despite the well-established association of thrombosis in patients with cancer, it is equally important to note that the risk for thromboembolic events varies widely across specific cancer subpopulations. The association of VTE incidence with certain types of cancer, such as pancreas and primary brain tumors, has been well studied [6]. Additional factors including patient age, ethnicity, comorbidities, specific therapeutic interventions, settings, and surgery also collectively influence the risk of VTE [7]. Pharmacologic thromboprophylaxis has been repeatedly proven to reduce VTE risk across various high-risk settings. Understanding risk of cancer-associated VTE is therefore highly important because optimizing thromboprophylaxis can best be achieved by targeting patients with cancer at high risk for VTE and avoiding prophylaxis in those at low risk for VTE. Of note, not as much is known about incidence, prediction, and prevention of ATE, but where known, these data have been highlighted. This review focuses on understanding optimal approaches to both risk prediction and patient selection for primary pharmacologic thromboprophylaxis of cancer-associated VTE.

Risk Prediction

Risk for cancer-associated VTE is multifactorial, and no single risk factor or biomarker can be used to best understand or predict risk [8]. Current guidelines recommend using the Khorana score to identify risk for cancer-associated VTE in patients with cancer initiating systemic therapy. This risk assessment tool was developed and validated more than a decade ago and has undergone multiple validation studies since its conception. It relies on five simple clinical and laboratory variables including type of cancer, components of the complete blood count, and body mass index (Table 1) [9]. Recent re-evaluations of the score suggest that the cutoff for high-risk VTE—set in the original publication as a score of 3 or higher—may be more optimally defined as a score of 2 or higher in both outpatients and hospitalized patients with cancer [10–12]. In particular, the first prospective validation of this score, led by the Vienna group, found a nearly 10% cumulative 6-month incidence of VTE in patients with a score of 2 [10]. These findings have led to the inclusion of patients with scores of 2 or higher in prospective trials of thromboprophylaxis, as we shall discuss later.

Table 1. Khorana score for prediction of cancer-associated VTE in the ambulatory setting [9]

Patient characteristics	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350 × 10^9/L	1
Hemoglobin level <10 mg/mL or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 × 10^9/L	1
BMI ≥35 kg/m^2	1

Original risk cutoffs are as follows: high-risk score, ≥3; intermediate-risk score, 1–2; low-risk score, 0. Newer trials of thromboprophylaxis have used score of ≥2 as eligibility criterion [31, 32].
Abbreviations: BMI, body mass index; VTE, venous thromboembolism.

Emerging studies have continued to optimize risk prediction approaches in patients with cancer [13, 14]. Several new or modified risk assessment tools have been proposed that include the addition of biomarkers, although many of these have not yet been validated and none have been used as eligibility criteria in trials of thromboprophylaxis (Table 2). The Khorana score has a high negative predictive value (i.e., is highly effective at identifying patients at low risk for VTE) but has a low positive predictive value. It may not be as predictive in individual specific cancers (e.g., lung cancer) because it was designed as a tool for a mixed solid tumor population. Hence, newer approaches are needed to better optimize risk–benefit ratios for individual patients with cancer. Biomarkers including D-dimer and tissue factor (either by activity or by antigen) and other risk factors have been proposed to either modify existing risk tools or be used alone to identify high-risk patients. D-dimer (with varying cutoff values) has been included as part of a newly developed risk tool and has greater data to support its use. Overall, however, data for biomarkers are conflicting, and individual biomarkers are not currently recommended for standalone use in clinical practice [15].

Specific risk tools have been recently developed for a niche population known to be at high risk for VTE: patients with multiple myeloma. In a large analysis, investigators combined significant variables to develop the IMPEDE VTE score (**I**mmunomodulatory agent; Body **M**ass Index ≥25 kg/m^2; **P**elvic, hip, or femur fracture; **E**rythropoietin stimulating agent; **D**examethasone/Doxorubicin; Asian **E**thnicity/Race; **V**TE history; **T**unneled line/central venous catheter; **E**xisting thromboprophylaxis) [16]. The score demonstrated satisfactory discrimination in the derivation cohort (C-statistic = 0.66). VTE risk significantly increased as the score increased (hazard ratio [HR], 1.20; $p < .0001$). In a separate analysis of older patients receiving immunomodulatory drug-based therapy, the SAVED risk score was developed, which includes five clinical variables: prior **s**urgery, **A**sian race, **V**TE history, age ≥80 years, and **d**examethasone dose [17]. The model stratified approximately 30% of patients in both the derivation and validation cohorts as high risk. HRs were 1.85 ($p < .01$) and 1.98 ($p < .01$) for high- versus low-risk groups in the derivation and validation cohorts, respectively.

Major knowledge gaps in risk stratification remain and warrant further analyses. Risk factors for ATE are not well understood and there are no risk tools for prediction of ATE. Cancer-associated ATE is increasingly recognized in specific malignancies and in association with the expanding classes of newer systemic therapy agents [18–20]. The pathobiology of ATEs in cancer is complex, and individual patient risk for an ATE entails a multifactorial interaction between cardiovascular risk factors and comorbidities, the specific malignancy, and

Table 2. Characteristics of select risk assessment tools for predicting VTE in patients with cancer

Risk score	Characteristics of variables/population included	External validation[a]	Used for selection of patients for thromboprophylaxis?
Khorana [9]	(original)	+++	Yes (retrospective) Yes (prospective randomized trials)
Vienna (2010) [10]	Adds D-dimer, sP-selectin	–	–
PROTECHT [29]	Removes BMI, adds chemotherapy	–	–
ONKOTEV [44]	Adds variables: metastatic disease, prior VTE, compression	–	–
COMPASS-CAT [45]	Breast, colorectal, lung, ovarian only	+ (lung)	–
Tic-ONCO [46]	Adds genetic risk factors	–	–
Pabinger et al. (2018) [13]	Adds D-dimer, removes all other variables except site	+	–
IMPEDE [16]	Multiple myeloma only	+	–
SAVED [17]	Multiple myeloma only	+	–

[a]The plus sign (+) refers to whether external validation was done or not. In the first row, several external validations were done, so signified by three plus signs (+++); the minus signs (–) indicate not done.
Abbreviations: BMI, body mass index; sP-selectin, soluble P-selectin; VTE, venous thromboembolism.

anticancer therapy. Treatment with several specific chemotherapeutic agents, immunomodulatory drugs, vascular endothelial growth factor pathway inhibitors, tyrosine kinase inhibitors, and radiotherapy impart an increased risk for ATEs. This risk results from specific therapy-related mechanisms and often involves endothelial injury.

The risk of thrombosis with hematologic malignancies other than myeloma represents another major knowledge gap. In a large analysis of a California registry, of 2,482 cases with acute lymphoblastic leukemia (ALL), the 2-year incidence of VTE in ALL was 4.5% [21]. Contemporary studies continue to show exceedingly high rates of VTE (including central nervous system thrombi) in patients with ALL, possibly related to regimens that contain asparaginase and glucocorticoids, with no clear mitigation strategy [22, 23]. Thrombosis can also be observed in patients with acute myelogenous leukemia (AML). In the California registry cited above, among 5,394 cases with AML, the 2-year cumulative incidence of VTE was 281 (5.2%) [21]. In a prospective cohort study, the prevalence of thrombosis was 8.7% (4.7% venous, 4.0% arterial) in younger adults over a median follow-up of 478 days and 10.4% (4.4% venous, 5.9% arterial) in elderly patients with AML [24]. Of note, in this study, blood samples were collected before the start of treatment in 410 patients with newly diagnosed AML. The following disseminated intravascular coagulation (DIC) parameters were determined: D-dimer, prothrombin time, antithrombin, fibrinogen, and α-2-antiplasmin. The DIC score according to the International Society on Thrombosis and Haemostasis scoring system for DIC was determined. The calculated DIC score has significantly predicted venous and arterial thrombosis with an HR for a high DIC score (≥5) of 4.79 (1.71–13.45). These results were confirmed in the validation cohort of elderly patients with AML (HR, 11.08; 95% confidence interval [CI], 3.23–38.06).

Bleeding is an important adverse effect of thromboprophylaxis, but there are no clear criteria for identifying patients at higher bleeding risk. Existing risk assessment tools for bleeding have not been studied specifically in the cancer population. In a large analysis of pooled U.S. health system data, bleeding incidence was higher in patients with cancer compared with those without cancer, regardless of the anticoagulant used [25]. Patients with gastrointestinal (GI) malignancies appeared to have a higher incidence of bleeding compared with other tumors across all anticoagulants. Other factors associated with an increased bleeding risk included metastatic disease, chronic kidney disease, and thrombocytopenia. Additional studies to specifically understand risk of bleeding in patients with GI malignancies are warranted.

Finally, it should be noted that patients with cancer are typically unaware that they are at higher risk of DVT and PE and are often uninformed about the warning signs and symptoms of VTE. Health care systems should therefore broaden efforts to improve patient education on cancer-associated thrombosis [26].

Primary Prevention Approaches

PROTECHT and SAVE-ONCO, two large outpatient trials, have previously addressed thromboprophylaxis across a spectrum of solid tumors but did not enroll patients based on risk [27, 28]. Although these trials were statistically significant in reducing VTE risk, clinical event rates were low, and these results did not translate into clinical practice recommendations. Proof of concept that a risk-based approach would lead to greater benefit from thromboprophylaxis for individuals at higher risk was obtained from results of the PHACS trial and a pooled analysis including high-risk subgroups of the PROTECHT and SAVE-ONCO trials (pooled relative risk for VTE with thromboprophylaxis was 0.41 [95% CI, 0.22–0.78; p = .006]) [29]. A recent individual patient-level meta-analysis of multiple randomized trials similarly evaluated the efficacy and safety of low-molecular-weight heparin (LMWH) in patients with a Khorana score ≥3 [30]. Among these high-risk patients, LMWH decreased the risk of VTE by 64% compared with placebo or observation (odds ratio, 0.36; 95% CI, 0.22–0.58). Together, these published

Table 3. Selecting ambulatory patients with cancer for pharmacologic thromboprophylaxis

Clinical setting	Pharmacologic thromboprophylaxis	Type of anticoagulant
High risk for VTE[a] - Low bleeding risk	Yes, for up to 6 months Reassess risk/benefit periodically	Apixaban 2.5 mg b.i.d. Rivaroxaban 10 mg OD Low-molecular-weight heparin OD
High risk for VTE[a] - High bleeding risk[b]	No Reassess periodically	—
Intermediate risk for VTE[c] - Low bleeding risk	No Reassess periodically	—
Intermediate risk for VTE[c] - High bleeding risk[b]	No	—
Low risk for VTE[d]	No	—

[a]High risk for VTE defined as Khorana score ≥2.
[b]High bleeding risk = upper gastrointestinal luminal cancers, severe thrombocytopenia (platelet count <50,000), creatinine clearance <30 mL/minute, history of severe bleeding diathesis (severe hemophilia, type 3 von Willebrand disease, severe thrombocytopathy), recent major bleeding (gastrointestinal <1 week; intracranial <3 weeks), use of dual antiplatelet therapy.
[c]Intermediate risk for VTE defined as Khorana score 1.
[d]Low risk for VTE defined as Khorana score 0.
Abbreviations: —, not applicable; OD, daily; VTE, venous thromboembolism.

data provided support for outpatient prophylaxis in patients with a Khorana score of ≥3. However, LMWHs are inconvenient, expensive (at least in the U.S.), and associated with burden of self-injection. Given these issues and the lack of "true" prospective data, risk-adapted thromboprophylaxis was not strongly recommended by guidelines initially.

Two recently published randomized trials have specifically addressed risk-adapted thromboprophylaxis using direct oral anticoagulants (DOACs): CASSINI, with rivaroxaban, and AVERT, with apixaban [31, 32]. Of 841 patients who underwent randomization in CASSINI, the primary endpoint occurred in 25 of 420 patients (6.0%) in the rivaroxaban group and in 37 of 421 (8.8%) in the placebo group (HR, 0.66; 95% CI, 0.40–1.09; $p = .10$) in the period up to day 180. In a prespecified intervention-period analysis, the primary endpoint occurred in 11 patients (2.6%) in the rivaroxaban group and in 27 (6.4%) in the placebo group (HR, 0.40; 95% CI, 0.20–0.80). Major bleeding occurred in 8 of 405 patients (2.0%) in the rivaroxaban group and in 4 of 404 (1.0%) in the placebo group (HR, 1.96; 95% CI, 0.59–6.49). In AVERT, VTE occurred in 12 of 288 patients (4.2%) in the apixaban group and in 28 of 275 patients (10.2%) in the placebo group (HR, 0.41; 95% CI, 0.26–0.65; $p < .001$). During the treatment period, major bleeding occurred in six patients (2.1%) in the apixaban group and in three patients (1.1%) in the placebo group (HR, 1.89; 95% CI, 0.39–9.24). A subsequent analysis of CASSINI comprising nonprimary endpoint thrombotic events (including ATE) confirmed that fewer patients randomized to rivaroxaban experienced thromboembolic events during the intervention period (13/420 patients [3.1%] vs. placebo 38/421 [9%]; HR, 0.33 [0.18, 0.62]; $p < .001$; number needed to treat [NNT] = 17) [33]. In a meta-analysis of these studies, the relative risk for overall VTE incidence by 6 months was 0.56 (0.35–0.89) [34]. There was increased risk of major bleeding and clinically relevant nonmajor bleeding while on treatment (1.96 [0.80–4.82] and 1.28 [0.74–2.20], respectively]. Patients with a high-risk Khorana score (≥3) derived the largest absolute VTE risk reduction.

A separate cost-effectiveness analysis of DOAC studies found that low-dose DOAC thromboprophylaxis for 6 months was associated with 32 per 1,000 fewer VTE and 11 per 1,000 more major bleeding episodes over a lifetime compared with placebo [35]. The incremental cost and quality-adjusted life-year (QALY) increases were $1,445 and 0.12, respectively, with an Institute for Clinical and Economic Review (ICER) evaluation of $11,947 per QALY gained. This strategy was 94% cost-effective at the threshold of $50,000 per QALY. The selection of patients with Khorana scores ≥3 yielded the greatest value, with an ICER of $5,794 per QALY gained. Since publication of these results, major guidelines have been revised to include DOAC thromboprophylaxis in patients with cancer at high risk for VTE [8, 36, 37]. A general approach to selecting patients for outpatient thromboprophylaxis is provided in Table 3 and includes individualized assessment of risks/benefits. Importantly, recommendations about thromboprophylaxis should be generated with the patient through a shared decision-making process and must encompass the patient's preferences and values.

Inpatient Thromboprophylaxis

Hospitalized patients with cancer are known to be at particularly high risk for VTE. There are some predictive risk tools that have been studied in this population, but none have been specifically designed for inpatients with cancer. Two retrospective cohort studies have established that a Khorana score of ≥2 is predictive of inpatient VTE as well [12, 38]. Although inpatient thromboprophylaxis is widely recommended by guidelines and is a quality metric for regulatory agencies, there are scant data to support its use. A meta-analysis of cancer subgroups from inpatient prophylaxis studies demonstrated no benefit in patients with cancer with usual doses of thromboprophylaxis [39]. A recent phase II randomized trial suggested high cumulative rates of VTE at day 17, despite usual doses of inpatient LMWH prophylaxis [40]. There are no large randomized trials to demonstrate benefit or risk of inpatient thromboprophylaxis specifically in patients with cancer, and studies suggest that inpatient prophylaxis is applied inconsistently across levels of risk [41]. The true benefit and risk of inpatient thromboprophylaxis in contemporary oncology deserves study in randomized clinical trials.

Implementing Outpatient Thromboprophylaxis

Although most cancer-associated VTE occurs in the outpatient setting, outpatient thromboprophylaxis has not been widely adopted in oncology for several reasons. First, initial trials of LMWH thromboprophylaxis showed low event rates and a high NNT to prevent one VTE [28]. In addition, LMWH is expensive in the U.S., and daily self-injections are inconvenient and further add to a patient with cancer's heavy burden of care. The DOAC trials have addressed some of these barriers given that DOACs are oral agents, less expensive than LMWHs in the U.S., and less burdensome for patients. However, several barriers remain. The data and guideline updates are relatively new, and education of cancer providers is necessary. Regulatory approval of one or more agents would be helpful as well. Finally, the interactions of DOACs and other anticoagulants with anticancer systemic therapy are incompletely understood.

Implementation science approaches are sorely needed. Innovative new models to improve compliance with risk prediction and thromboprophylaxis have recently been piloted at major institutions. In Canada, investigators developed an innovative computerized system that automatically accesses electronic medical records (EMRs) and uses the Khorana score to calculate real-time VTE risk in patients with active cancer [26]. The authors were able to identify intermediate- to high-risk patients appropriately and provide these patients with additional educational material regarding risk of VTE. A similar EMR tool was developed by investigators in the U.S. to identify high-risk patients for early detection. To better comply with new guidelines, this tool is currently being refashioned to recommend prophylaxis [42]. Most recently, U.S. investigators developed and deployed a model of care for VTE prevention in an outpatient clinic that included nurses, advanced practice providers, pharmacists, hematologists, oncologists, and the EMR to increase compliance with guidelines [43]. This program prospectively identified high-risk patients using the Khorana and PROTECHT scores (≥3 points) using an electronic tool. Patients with a predicted high risk of VTE during treatment were offered a hematology consultation to consider VTE prophylaxis. Of more than 900 evaluated patients, VTE monthly education rates increased from <5% before program initiation to 81.6% (SD, 11.9) during the implementation phase and 94.7% (SD, 4.9) for the full 2-year postimplementation phase. Referrals to hematology were offered to 151 patients (71%), with 141 patients (93%) being assessed and 93.8% receiving VTE prophylaxis. Thus, this multidisciplinary program sustainably increased VTE education and risk assessment rates from <5% at baseline to >95% and led to substantially greater consideration for thromboprophylaxis in outpatients with cancer. Health systems need to carefully consider these various models for feasibility of adoption in local practice.

Conclusion

The following are clinical takeaways: (a) Develop a health system-based approach to identifying patients at high risk for VTE. Based on current guidelines, "high risk" should be defined as patients with a Khorana score of 2 or higher. Approaches can include alerts in the EMR, structured referral to hematology consult services or cancer pharmacists, and education of oncology providers. (b) All patients with cancer, and specifically high-risk patients, should receive education about the warning signs and symptoms of VTE. (c) High-risk patients who are not at risk for major bleeding (no recent or ongoing bleeding, not on dual antiplatelet therapy, no luminal primary gastroesophageal cancer) should be considered for thromboprophylaxis with a DOAC (rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily). For patients with drug–drug interactions with a DOAC or with primary gastroesophageal cancers, LMWH could be considered as an alternative.

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