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Prevention and Treatment of Cancer-Associated Venous Thromboembolism: a Review

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Abstract

Purpose of review Patients with cancer have an increased risk of venous thromboembolism (VTE). Cancer-associated VTE is associated with an increased risk of morbidity and mortality. Treatment of VTE in cancer is associated with higher rates of recurrent thrombosis as well as major bleeding compared with the general population. The goal of this review is to provide a summary of current evidence for the prevention and treatment of cancer-associated VTE.
Recent findings Validated risk prediction models are available to aide clinicians in identifying patients with cancer with the highest risk of VTE. Those patients with intermediate to high risk of VTE may benefit from primary prophylaxis with apixaban or rivaroxaban. Low-molecular-weight heparin is superior to vitamin K antagonists for the treatment of cancer-associated VTE. There is mounting evidence to support use of the direct oral anticoagulants for VTE in patients with cancer.
Summary Decisions on type and duration of anticoagulation in patients with cancer, either for primary or secondary prevention, should be made on a case-by-case basis with taking into account the individual patient bleeding and thrombotic risk.

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Introduction

Cancer associated venous thromboembolism (VTE) is a prevalent disease, accounting for 20–30% of all thrombotic events [1, 2]. In patients with cancer, the risk of developing VTE is 4- to 7-fold higher compared with patients without cancer [3, 4]. The rate of cancer-associated VTE continues to rise and doubled over a decade of observation [4]. In addition, the incidence of VTE at autopsy in patients with cancer is estimated to be even higher (up to 35%) than that cited in observational studies [5].

Cancer-associated VTE is associated with increased morbidity and mortality. Second only to the underlying malignancy, VTE is a leading cause of death in cancer patients [6]. Patients with cancer and VTE have a 3-fold increased risk of death compared with those with cancer and no VTE [7]. Furthermore, treatment of VTE in patients with cancer is associated with increased risk of complications and can delay cancer treatment. The rate of recurrent VTE despite anticoagulation is 3-fold higher in patients with cancer compared with those without [8]. In addition, the risk of hemorrhage on anticoagulation is higher in patients with cancer [8].

The risk of VTE in cancer varies by individual patient factors as well as with histology. Knowledge of this has led to the development and validation of several risk models to predict VTE in patients with cancer [9–12]. Among them, the Khorana score is the most validated in ambulatory cancer patients [9] and is recommended by the American Society of Clinical Oncology VTE Prophylaxis and Treatment Guidelines [13]. While current guidelines do not recommend routine primary prophylaxis for VTE in cancer, evidence is emerging showing safety and efficacy of this strategy.

Recent studies have focused on both primary and secondary thromboprophylaxis in patients with cancer. Primary thromboprophylaxis has the potential to reduce morbidity and mortality of cancer-associated VTE. In addition, use of direct oral anticoagulants (DAOCs) for the treatment of VTE in patients with cancer is rising. The aim of this review is to review current evidence for the prevention and treatment of cancer-associated VTE.

Prevention of venous thromboembolism in unselected ambulatory cancer patients

Given the risk of VTE in cancer and the associated morbidity and mortality, several studies assessed the efficacy of primary prophylaxis in ambulatory cancer patients. In a trial of patients with metastatic breast cancer, there was a reduction in risk of VTE with very low-dose warfarin (INR goal 1.3–1.9) versus placebo (0.7% versus 4.4%, $p = 0.03$) [14]. However, this small study ($n = 311$) was deemed insufficient to change routine practice guidelines [15, 16]. The PROTECHT study evaluated the efficacy of nadroparin, a LMWH, against placebo for the prevention of arterial or venous thromboembolic events in 1150 ambulatory cancer patients with solid tumors [17]. Patients included had locally advanced or metastatic lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer and received treatment for up to 4 months. While nadroparin was shown to significantly reduce thromboembolic events compared with placebo (2% versus 3.9%, $p = 0.02$), the low event rate even in the placebo arm made clinicians question the degree of benefit and prompted further studies to focus on higher risk populations. Subsequently, the SAVE-ONCO trial focused on ambulatory patients with cancers associated with higher risk of VTE including metastatic or locally advanced lung, pancreatic, gastric, colorectal, bladder, or ovarian cancer [18]. Patients received semuloparin or placebo for at least the first 3 months of chemotherapy. While semuloparin was associated with a significant reduction in VTE (1.2% versus 3.4%, $p < 0.001$),

the low event rate remained a barrier to practice change. A meta-analysis combining these two trials in addition to several similar trials confirmed the efficacy of primary prophylaxis with LMWH (RR 0.54; 95% confidence interval (CI) 0.38–0.75) and showed no significant increased risk of major bleeding (risk ratio (RR) 1.44; 95% CI 0.98–2.11) [19]. However, while primary prophylaxis is effective in these studies, the low thrombotic rate in the placebo arms, concern of bleeding risk associated with anticoagulation, and the morbidity and cost of daily injections all prevented adoption of routine primary prophylaxis in unselected ambulatory cancer patients, promoting further efforts to focus on identification of higher risk groups.

Predicting risk of cancer-associated venous thromboembolism

Several risk prediction models are available to quanitfy the risk of VTE in ambulatory cancer patients [9–12]. The Khorana score contains five predictor variables: [1] site of cancer, [2] platelet count, [3] white blood count (WBC), [4] hemoglobin level or use of erythropoietin stimulating agents (ESA), and [5] body mass index (BMI). Point assignment for each variable is as follows: [1] site of cancer (2 points gastric or pancreatic, 1 point lung, lymphoma, gynecologic, or genitourinary (excluding prostate) cancer); [2] platelet count ≥ 350,000/mm [3] (1 point); [3] WBC > 11,000/mm^3 (1 point); [4] hemoglobin < 10 g/dL or use of ESAs (1 point); and [5] BMI ≥ 35 kg/m^2 (1 point). Based on total points, the Khorana score separates patients into three risk groups: low risk (0 points), intermediate risk (1–2 points), and high risk (≥ 3 points). Patients in the high-risk group had a rate of VTE of 7%, intermediate risk 2%, and low risk < 1% over a mean follow-up of 73 days. External validations of the score confirmed the ability of the score to discriminate risk of VTE [10, 11]. Other risk scores have attempted to improve discrimination through modification of the Khorana score or by simplification of predictor variables. The Vienna modification assessed improvement through addition of two variables, D-dimer and soluble P-selectin [10]. Patients with elevated D-Dimer and/or soluble P-selectin received one point for each elevated value. This resulted in a modification of risk groups with high risk having ≥ 5 points, intermediate risk having 3 points, and the lowest risk group having 0 points. Compared with the Khorana score, the Vienna modification resulted in an improvement in positive predictive value from 22.1 (Khorana score) to 42.9%. However, lack of availability of soluble P-selectin testing in routine clinical practice serves as a barrier for implementation of this model. The PROTHECT score assessed the addition of treatment variables by adding one point each for treatment with platinum or gemcitabine chemotherapy [12]. Recently, Pabinger et al. developed a simplified model, the CATS nomogram, to assess risk of VTE in cancer [11]. This model uses two clinical variables to assess risk of VTE, D-dimer and site of cancer. Site of cancer resulted in a designation of very high risk (pancreatic or gastric), high risk (lung, colorectal, esophageal, lymphoma, genitourinary excluding prostate, gynecologic), or low/intermediate risk (breast or prostate). Patients receive 0–200 points based on a correlating nomogram with the highest points having a 6-month cumulative incidence of VTE of 29%, compared with 2% in those with 0 points. Among the available risk models, the American Society of Clinical Oncology recommends use of the Khorana score, to assess VTE risk and provide

risk counseling to ambulatory cancer patients [9, 13]. Until recently, the clinical risk scores have not been used to guide strategies of primary thromboprophylaxis.

Prevention of venous thromboembolism in high-risk ambulatory cancer patients

A combination of validated risk prediction models and the ease of administration of DOACs prompted studies to assess the efficacy of DOACs for prevention of VTE in ambulatory cancer patients. The AVERT study assessed the efficacy and safety of apixaban for prevention of VTE in ambulatory cancer patients with intermediate to high risk of VTE, identified by a Khorana score of ≥ 2 points. In this double-blind trial, 574 patients were randomized to apixaban 2.5 mg oral twice daily versus placebo for treatment duration of 180 days [20]. The primary efficacy outcome was objectively confirmed proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). Apixaban was associated with a significant reduction in the risk of VTE compared with placebo (4.2% versus 10.2%, hazard ratio (HR) 0.41; 95% CI 0.26–0.65). However, there was an increased risk of major bleeding with apixaban compared with placebo (3.5% versus 1.8%, HR 2.00; 95% CI 1.01–3.95). This difference was not significant in the on-treatment analysis (only including events occurring while on study drugs or up to 2 days after last dose of study drugs) (2.1% versus 1.1%, HR 1.89; 95% CI 0.39–9.24). There were no deaths attributed to major bleeding in the study.

Similarly, the CASSINI trial assessed the efficacy of rivaroxaban 10 mg daily for prevention of VTE in a double-blind, placebo-controlled, randomized trial in the same population of patients (ambulatory cancer patients with a Khorana score of ≥ 2 initiating a new line of chemotherapy) [21]. Patients ($n = 841$) received treatment for 180 days. The primary efficacy outcome was a composite endpoint of [1] objectively documented proximal lower extremity DVT or PE, [2] symptomatic DVT in the upper extremity or distal lower extremity, and [3] death attributed to VTE. Patients underwent screening ultrasound at baseline and weeks 8, 16, and 24. There was a trend towards a reduction in the risk of the primary efficacy outcome with rivaroxaban (6.0% versus 8.8%, HR 0.66; 95% CI 0.40 to 1.09). On treatment analysis revealed a significant reduction in the primary outcome associated with rivaroxaban (2.6% versus 6.4%, HR 0.40; 95% CI 0.20–0.80). While there was no significant difference in major bleeding between rivaroxaban and placebo (2.0% versus 1.0%, HR 1.96; 95% CI 0.59–6.49), there was one death attributed to major bleeding in the rivaroxaban arm. A summary of clinical trials with at least 200 patients evaluating primary thromboprophylaxis in patients with cancer is listed for reference in Table 1.

Initial treatment of cancer-associated venous thromboembolism

Historically, vitamin K antagonists (VKA) were the mainstay of therapy for cancer-associated VTE. However, in 2002, published results from a study showed both higher risk of hemorrhage as well as higher rate of anticoagulation failure in patients with cancer-associated VTE on VKA compared with the general population [8]. In this study, patients with cancer had 2.2-fold increased

Table 1. Summary of studies for Prevention of Cancer Associated Venous Thromboembolism*

	Prophylaxis	Comparator	Duration	Outcomes	Prophylaxis	Comparator	RR (95% CI)
Hass et al. [19, 44] (2012)	Certoparin	Placebo	6 months	Symptomatic VTE Major Bleeding	1.8% (8/442) 2.9% (13/447)	3.2% (14/441) 1.3% (6/451)	0.57 (0.24, 1.35) 2.19 (0.84, 5.70)
Kakkar et al. [19, 45] (2004)	Dalteparin	Placebo	12 months	Symptomatic VTE Major Bleeding	2.1% (4/190) 0.5% (1/190)	2.7% (5/184) 0.0% (0/184)	0.77 (0.21, 2.84) 2.91 (0.12, 70.87)
Pelzer et al. [19, 46] (2015)	Enoxaparin	No Treatment	3 months	Symptomatic VTE Major Bleeding	6.3% (10/160) 8.1% (13/160)	14.5% (22/152) 6.6% (10/152)	0.43 (0.21, 0.88) 1.24 (0.56, 2.73)
Agnelli et al. [18, 19] (2012)	Semuloparin	Placebo	3.5 months (median)	Symptomatic VTE Major Bleeding	0.7% (11/1608) 1.2% (19/1589)	2.1% (34/1604) 1.1% (18/1583)	0.32 (0.15–0.62)^ 1.05 (0.55, 2.04)+
Agnelli et al. [17, 19] (2009)	Nadroparin	Placebo	3 months (median)	Symptomatic VTE Major Bleeding	1.4% (11/769) 0.7% (5/769)	2.9% (11/381) 0.0% (0/381)	0.50 (0.22, 1.13)^ 5.46 (0.30, 98.43)^
Carrier et al. [20] (2019)	Apixaban	Placebo	6 months	Major VTE Major Bleeding	4.2% (12/288) 3.5% (10/288)	10.2% (28/275) 1.8% (5/275)	0.41 (0.26, 0.65)^ 2.00 (1.01, 3.95)^
Khorana et al. [21] (2019)	Rivaroxaban	Placebo	6 months	Major VTE Major Bleeding	5.7% (24/420) 2.0% (8/405)	8.1% (34/421) 1.0% (4/404)	0.71 (0.43, 1.17) 1.96 (0.59, 6.49)^

*Studies containing at least 200 patients, ^Hazard Ratio, +Odds Ratio, RR = Risk Ratio, CI = Confidence Interval, VTE = Venous Thromboembolism, NS = Not Specified), Major VTE = Objectively documented proximal deep vein thrombosis or pulmonary embolism (symptomatic or asymptomatic)

risk of major bleeding compared with patients with VTE without cancer (12.4% versus 4.9%, HR 2.2; 95% CI 1.2–4.1). In addition, cancer patients with VTE had a greater risk of recurrent thrombosis compared with non-cancer patients (20.7% versus 6.8%, HR 3.2; 95% CI 1.9–5.4). Therefore, subsequent trials compared the safety and efficacy of LMWH versus VKA in patients with cancer-associated VTE. The pivotal trial, the CLOT trial, revealed a 50% reduction in the risk of recurrent VTE with LMWH versus VKA (HR 0.48; 95% CI 0.30–0.77) with no increased risk of major bleeding ($p = 0.27$) [22]. Contrary to these findings, a subsequent randomized controlled trial compared treatment with the LWMH tinzaparin versus VKA in cancer-associated VTE [23]. While this population had fewer patients with metastatic disease compared with the CLOT trial, the investigators found no reduction in the risk of recurrent VTE with tinzaparin compared with VKA (7.2% versus 10.5%; HR 0.65; 95% CI 0.41–1.03). A meta-analysis of six randomized controlled trials [22–27] comparing LMWH with VKA found an overall reduction in risk of recurrent VTE with LMWH (odds ratio (OR) 0.55; 95% CI 0.40–0.75) with no increased risk in bleeding (RR 1.10; 95% CI 0.71–1.69) [28]. Based on the clinical evidence, guidelines recommended LWMH as the treatment of choice for patients with cancer-associated VTE [13, 29, 30].

Despite guideline recommendations, analyses of treatment patterns revealed persistent use of VKA as the treatment of choice for cancer-associated VTE. One study noted that while LWMH use increased from 2000 to 2007, only 31% of the patient population received LWMH monotherapy at the end of the study period with analysis over the duration of the study period showing that VKA was the treatment of choice for the majority of patients [31]. Practice patterns remained relatively unchanged from 2009 to 2014 during which time VKA remained the most commonly used anticoagulant for cancer-associated VTE [32]. Reasons for poor adoption of guidelines included burden of daily injections as well as high cost of LMWH. Over the past decade, the DOACs have shifted the treatment paradigm for treatment of VTE in patients without cancer. Studies show that these agents are non-inferior to VKA for prevention of recurrent VTE and are often associated with a reduced risk of major bleeding compared with VKA in patients without cancer [33–35]. A meta-analysis of 973 patients with cancer include in the pivotal DOAC trials found a signal for efficacy and safety of the DOACs in patients with cancer [36]. Recurrent VTE with DOACs was 4.1% compared with 6.1% with VKA (RR 0.66; 95% CI 0.38–1.2). In addition, there was no significant difference in the rates of bleeding (15% versus 16%, RR 0.94; 95% CI 0.70–1.3). These results combined with real-world practice patterns prompted prospective investigation into use of the DOACs in cancer-associated VTE.

Currently, three prospective, randomized controlled trials have been reported evaluating the safety and efficacy of the DOACs compared with LMWH for the treatment of cancer-associated VTE [37–39]. Hokusai VTE Cancer randomized 1050 cancer patients to edoxaban 60 mg daily (after at least 5 days of LMWH) versus standard dose dalteparin (200 IU/kg for 1 month followed by 150 IU/kg daily) [37]. The primary outcome event, composite of recurrent VTE or major bleeding during the 12-month study period, showed that edoxaban was non-inferior to dalteparin (12.8% versus 13.5%, HR 0.97; 95% CI 0.70–1.36, $p = 0.006$ for non-inferiority). There was a statistically higher rate of major bleeding associated with edoxaban compared with dalteparin (6.9% versus

4.0%, HR 1.77; 95% CI 1.03–3.04). A subgroup analysis found an interaction between gastrointestinal cancer and major bleeding with edoxaban compared with dalteparin ($p = 0.02$ for interaction). Similarly, the Select-D trial evaluated rivaroxaban (15 mg twice daily for 21 days followed by 20 mg once daily) versus standard dose dalteparin in the treatment cancer-associated VTE [38]. The 6-month cumulative rate of VTE recurrence was 4% with rivaroxaban compared with 11% with dalteparin (HR 0.43; 95% CI 0.19–0.99). The rate of major bleeding at 6 months was 6% for rivaroxaban compared with 4% for dalteparin (HR 1.83; 95% CI 0.69–4.96) with the corresponding rates of clinically relevant non-major bleeding 13% versus 4% (HR 3.76; 95% CI 1.63–8.69). As previously, the risk of major bleeding with rivaroxaban was higher in patients with esophageal and gastroesophageal cancers. Most recently, the results of the ADAM-VTE study were presented in abstract format, randomizing patients with cancer-related thrombosis to apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) versus standard dose dalteparin [39]. In this study, there was no significant difference in the rate of major bleeding (primary outcome) with apixaban (0%) versus dalteparin (2.1%) ($p = 1.00$). There was a reduction in the risk of recurrent VTE associated with apixaban (3.4% versus 14.1%, HR 0.26; 95% CI 0.09–0.80). While the results were promising, this study was small in sample size and was not yet published as a full manuscript, so the results are preliminary and would be pre-mature to adapt into routine practice. The ongoing CARAVAGGIO study is an international randomized, placebo-controlled study comparing apixaban with dalteparin in 1200 patients with cancer-associated VTE and could provide a more definitive answer when it is complete. A summary of clinical trials comparing treatment options for cancer-associated VTE is listed in Table 2.

Summary

In summary, patients with cancer have an increased risk of VTE, with rates of VTE rising. VTE is associated with increased risk of morbidity and mortality in patients with cancer [3, 4]. In addition, treatment of cancer-associated VTE is associated with both rates of higher recurrent VTE as well as bleeding compared with the general population [8]. Primary and secondary prevention of VTE have the potential to improve outcomes in this growing population.

Evidence supporting a role for anticoagulation in the primary prevention of cancer-associated VTE is growing. The development of current guidelines occurred prior to the results of the most recent AVERT and CASSINI trials [9, 40–42]. Thus, these guidelines do not recommend routine use of primary thromboprophylaxis for ambulatory cancer patients. With new data supporting the role of thromboprophylaxis, providers should be encouraged to assess each patient's thrombotic and bleeding risk. Several validated risk prediction tools exist to quantify a patient's thrombotic risk [9–12]. Decisions to use pharmacologic thromboprophylaxis should occur on a case-by-case basis after a risk-benefit discussion, taking into account patient preferences. Future guidelines will aid in decision analysis for this population.

High-level evidence supports the superiority of LMWH over VKA in patients with cancer, showing a decrease in risk of recurrent VTE with no increase in risk of major bleeding [28]. There are now three randomized controlled trials

Table 2. Summary of studies for Treatment of Cancer Associated Venous Thromboembolism*

	Treatment	Comparator	Duration	Outcomes	Treatment	Comparator	RR (95% CI)
Lee et al. [22, 47] (2003)	Dalteparin	Warfarin	6 months	Symptomatic VTE Major Bleeding	8.0% (27/336) 6.0% (19/338)	15.8% (53/336) 4.0% (12/335)	0.48 (0.30, 0.77)^ 1.60 (0.77, 3.36)
Hull et al. [25, 47] (2006)	Tinzaparin	Warfarin	3 months	Symptomatic VTE Major Bleeding	6.0% (6/100) 7.0% (7/100)	>10.0% (10/100) 7.0% (7/100)	0.60 (0.23, 1.59) 1.00 (0.34, 28.12)
Lee et al. [23, 47] (2015)	Tinzaparin	Warfarin	6 months	Symptomatic VTE Major Bleeding	6.9% (31/449) 2.7% (12/449)	10.0% (45/451) 2.4% (11/451)	0.65 (0.41, 1.03)^ 0.89 (0.40, 1.99)^
Raskob et al. [37] (2018)	Edoxaban	Dalteparin	6–12 months	Symptomatic VTE Major Bleeding	7.9% (41/522) 6.9% (36/522)	11.3% (59/524) 4.0% (21/524)	0.71 (0.48–1.06)^ 1.77 (1.03, 3.04)^
Young et al. [38] (2018)	Rivaroxaban	Dalteparin	6 months	Symptomatic VTE Major Bleeding	3.9% (8/203) 3.0% (6/203)	8.9% (18/203) 5.4% (11/203)	0.43 (0.19, 0.99)^ 1.83 (0.68, 4.96)^
McBane et al. [39] (2018)	Apixaban	Dalteparin	6 months	Major VTE Major Bleeding	3.4% (5/142) 0.0% (0/142)	14.1% (20/145) 2.1% (3/145)	0.26 (0.09, 0.80)^ 0.00 (0.0,)^

*Studies containing at least 200 patients, ^Hazard Ratio, +Odds Ratio, RR = Risk Ratio, CI = Confidence Interval, VTE = Venous Thromboembolism, NS = Not Specified), Major VTE = Objectively documented proximal deep vein thrombosis or pulmonary embolism (symptomatic or asymptomatic)

assessing DOACs versus LWMH in patients with cancer [37–39]. These trials support a role for DOACs in the treatment of cancer-associated VTE; however, also found the DOACs to be associated with a higher risk of major bleeding. Subgroup analyses of major bleeding risks suggest that patients with gastrointestinal cancers may harbor the largest risk. Based on the available evidence, some experts recognize a role for the use of DOACs in patients with cancer and VTE [43]. The duration of anticoagulation in cancer-associated VTE is unclear. The majority of current trials evaluated an initial treatment period of 6 months. After the initial treatment period, the decision to continue anticoagulation should be made on a patient-by-patient basis, individualizing the decision based on each patient's bleeding and thrombotic risks factors as well as patient preference.

Compliance with Ethical Standards

Conflict of Interest

Kristen Sanfilippo was on the Bristol-Myers Squibb speaker bureau, served on an advisory board for Pfizer and Bayer, received travel expenses from AstraZeneca, and received research funding from NHLBI.
Tzu-Fei Wang received consulting fees and travel expenses from Daiichi Sankyo and Pfizer.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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