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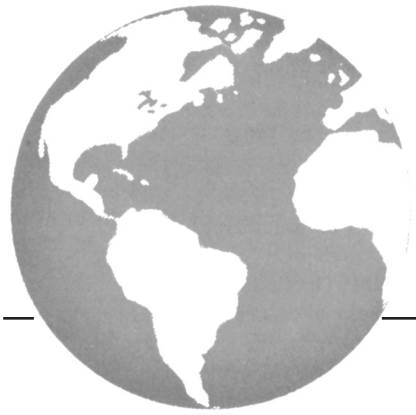
PRACTICE GUIDELINE



Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 1: prophylaxis

J.C. Easaw MD PhD, M.A. Shea–Budgell MSc,* C.M.J. Wu MD,* P.M. Czaykowski MD,† J. Kassis MD,‡ B. Kuehl PhD,§ H.J. Lim MD PhD,‖ M. MacNeil MD,# D. Martinusen PharmD,‖ P.A. McFarlane MD PhD,§ E. Meek RN,* O. Moodley MD,** S. Shivakumar MD,# V. Tagalakis MD,‡ S. Welch MD,§ and P. Kavan MD‡*

ABSTRACT

Patients with cancer are at increased risk of venous thromboembolism (VTE). Anticoagulation therapy has been shown to prevent VTE; however, unique clinical circumstances in patients with cancer can often complicate the decisions surrounding the administration of prophylactic anticoagulation. No national Canadian guidelines on the prevention of cancer-associated thrombosis have been published. We therefore aimed to develop a consensus-based, evidence-informed guideline on the topic.

PubMed was searched for clinical trials and meta-analyses published between 2002 and 2013. Reference lists of key articles were hand-searched for additional publications. Content experts from across Canada were assembled to review the evidence and make recommendations.

Low molecular weight heparin can be used prophylactically in cancer patients at high risk of developing VTE. Direct oral anticoagulants are not recommended for VTE prophylaxis at this time. Specific clinical scenarios, including renal insufficiency, thrombocytopenia, liver disease, and obesity can warrant modifications in the administration of prophylactic anticoagulant therapy. There is no evidence to support the monitoring of anti–factor Xa levels in clinically stable cancer patients receiving prophylactic anticoagulation; however, factor Xa levels could be checked at baseline and periodically in patients with renal insufficiency. The use of anticoagulation therapy to prolong survival in cancer patients without the presence of risk factors for VTE is not recommended.

KEY WORDS

Low molecular weight heparin, prophylaxis, anticoagulation, venous thromboembolism, pulmonary embolism, deep vein thrombosis, clots, practice guideline

1. INTRODUCTION

Patients with cancer are at increased risk of developing venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism[1,2]. Hypercoagulability in this population can occur as a result of cancer treatment (particularly chemotherapy) and of the cancer itself[3,4]. Compared with patients having local disease, those with metastatic disease have a significantly higher risk of developing VTE[5].

The approximate annual incidence of VTE in cancer patients treated with chemotherapy is estimated at 1 in 200; in the general population, the estimate is 117 in 100,000[6]. Importantly, data show that the incidence of VTE in cancer patients is on the rise, possibly because of longer survival and the older age of cancer patients[7]. Table I summarizes several patient-, cancer-, and treatment-related factors that adversely affect the risk of VTE[8,9]. The risk of dying after an acute thrombotic event is higher by a factor of 4 to 8 in cancer patients than in patients without cancer, and VTE is the second-leading cause of non-cancer death in cancer patients[8–13].

Although several pharmacologic agents are available to prevent VTE, administration of anticoagulants is not always straightforward in the oncology setting. Patients with cancer undergo complex treatment protocols and could have other comorbidities such as renal or hepatic insufficiency and thrombocytopenia that can affect the efficacy and safety of anticoagulation. Several groups have published guidelines on the management of VTE in oncology patients—most recently, the American Society of Clinical Oncology[14] and CancerControl Alberta (part of Alberta Health Services)[15]. Other published guidelines include those from the U.S. National Comprehensive Cancer Network[16], the European Society for Medical Oncology[17], and the American College of Chest Physicians[18].

Despite the wealth of guidelines, several key issues surrounding the use of prophylactic anticoagulation and its monitoring in specific subpopulations have

TABLE I Factors associated with venous thromboembolism in patients w ith cancer

Category	*Factors*
Patient-related	• Increased age • Ethnicity (higher risk in African Americans) • Comorbid conditions (infection, renal and pulmonary disease, arterial thromboembolism, venous thromboembolism history, inherited prothrombotic mutations) • Obesity • Performance status
Cancer-related	• Site of primary cancer • Stage (risk increases with higher stage) • Comorbid conditions • Histology • Time since diagnosis (risk increases during first 3–6 months)
Treatment-related	• Chemotherapy, antiangiogenesis agents, hormonal therapy • Radiation therapy • Surgery lasting 60 minutes or more • Erythropoiesis-stimulating agents, transfusions • Indwelling venous access
Biochemical	• Leukocyte count exceeding 11×10^9/L • Hemoglobin below 100 g/L

not been addressed. Moreover, most of the existing guidelines are largely general oncology guidelines with a subsection on VTE. No national guidelines are specifically dedicated to the prophylaxis of cancer-associated VTE.

Our overall aim was to develop national recommendations that are evidence-based (or consensus-based where evidence is lacking) on the prevention of VTE in patients with cancer. The recommendations are meant to provide guidance to physicians, nurses, and other frontline medical professionals involved in the management of patients with cancer. We address VTE prophylaxis in ambulatory, hospitalized, and surgical patients, and the use of anticoagulation in specific clinical scenarios such as renal and hepatic insufficiency, brain metastases, and thrombocytopenia. We also discuss the use of anticoagulation to prolong survival and the monitoring of anticoagulation therapy.

2. METHODS

2.1 Literature Search Strategy

The U.S. National Library of Medicine's PubMed database was searched for relevant articles published between 2002 and March 2013. Search terms included "neoplasm" or "cancer" and "thrombosis prophylaxis" or "VTE prophylaxis," and results were limited to randomized controlled trials (RCTs) and meta-analyses published between 2008 and March 2013. Trials that did not report outcomes related to the prophylaxis of VTE were excluded. In addition, the U.S. National Guidelines Clearinghouse was searched for guidelines published between 2007 and March 2013. Updated results of relevant clinical trials published after March 2013 were also included. Because of a lack of translation services, non-English-language articles were excluded from the review of the evidence.

2.2 Development of Recommendations

The development and review process for the recommendations was modelled after these sources: the U.K. National Institute for Health and Clinical Excellence[19], the *Archives of Pediatrics and Adolescent Medicine*[20], and the AGREE collaboration[21]. Clinical questions and initial recommendations were developed by two medical oncologists (JCE and PK) and a cancer research methodologist (MAS) based on clinical experience and the literature review. The University of Oxford Centre for Evidence-Based Medicine grading system was used to grade the recommendations[22]. Briefly, the levels of evidence were these:

- Level 1: a systematic review of homogenous RCTs or a single RCT with a narrow confidence interval
- Level 2: a systematic review of homogenous cohort studies, or an individual cohort study or a low-quality RCT
- Level 3: a systematic review of case–control studies or an individual case–control study
- Level 4: case series and poor-quality cohort and case–control studies
- Level 5: expert opinion without explicit critical appraisal

These grades were defined:

- Grade A: consistent level 1 studies
- Grade B: consistent level 2 or 3 studies or extrapolations from level 1 studies
- Grade C: level 4 studies or extrapolations from level 2 or 3 studies
- Grade D: inconsistent or inconclusive studies of any level

The recommendations were reviewed by an expert panel of medical oncologists, hematologic oncologists, hematologists, and an internist, representing the provinces of Nova Scotia, Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia. A total of 11 specialists contributed directly to the development of all recommendations. Recommendations pertaining to renal insufficiency

were further reviewed by a nephrologist and a pharmacist with expertise in renal insufficiency.

Recommendations were initially reviewed using a Web-based survey to capture the level of agreement with each statement on a 5-point scale ranging from "strongly agree" to "strongly disagree" and including an option of "unsure." An evidence summary accompanied each statement, and panelists were instructed to consider the level of evidence when rating each statement. In addition to the rating scales, panelists were given the opportunity to comment on each statement. Based on panelist responses, recommendations were categorized as "consensus" (that is, statements with which most panelists agreed, with no more than 3 "neutral" or "unsure" responses allowed) or "non-consensus" (that is, statements with which at least 1 panelist disagreed or those that had 4 or more "neutral" or "unsure" responses). Non-consensus statements were reviewed once with the entire panel via webinar (Cisco WebEx, San Jose, CA, U.S.A.) to better understand the rationale for any disagreement or uncertainty and to determine where additional discussion was needed to reach consensus. The non-consensus statements were divided into two categories: "monitoring and dosing" and "special populations." Panel members were assigned to working groups to address statements in one of the two categories. Working groups met a final time via webinar to discuss and revise the statements; consensus methods were used.

3. RESULTS

The literature review identified sixty-five publications, including three clinical practice guidelines. Meta-analyses and RCTs were considered strong (higher-level) evidence in developing the recommendations. Several relevant retrospective case series were also included in the discussion, but were considered to be weak (lower-level) evidence. Based on the Web survey responses, consensus was reached immediately on 15 of the 22 final recommendation statements (68%). The remaining 7 recommendations were further discussed by the assigned panel members to reach consensus. Consensus was eventually reached for all 22 recommendation statements (Table II).

4. DISCUSSION

Patients with active malignancy are at increased risk of VTE and increased risk of VTE-related mortality[10,12,13]. Successful prevention of VTE is a high priority, and DVT prophylaxis in the general population has been well established in multiple medical and surgical populations[18].

4.1 Prophylaxis in Ambulatory Cancer Patients

None of the current guidelines recommend routine thromboprophylaxis in ambulatory cancer patients, but all suggest that it be considered for very select high-risk patients[14,16,17]. The outpatient prophylaxis score developed by Khorana *et al.*[4] (Table III) and validated in randomized trials identifies cancer patients at risk for VTE. Anticoagulants tested in cancer patients include dalteparin, enoxaparin, tinzaparin, semuloparin, certoparin, bemiparin, nadroparin, and warfarin[23–42], of which enoxaparin, dalteparin, and tinzaparin are readily available in Canada. A Cochrane systematic review[43] of 21 RCTs that included 9861 ambulatory patients with cancer receiving chemotherapy showed that, compared with inactive control and warfarin, low molecular weight heparin (LMWH) was associated with a 45% reduction in the overall VTE incidence [risk ratio: 0.55; 95% confidence interval (CI): 0.34 to 0.88; $p < 0.05$] and a nonsignificant increase in bleeding. Despite those very interesting findings, which accord with other major guidelines, our consensus was that prophylactic anticoagulation is not advised for all outpatients, but can be used in select cases where indicated.

4.2 Prophylaxis in Hospitalized Cancer Patients

Most hospitalized patients with cancer require thromboprophylaxis throughout hospitalization[14–16,18]. A systematic review comparing LMWH, unfractionated heparin (UFH), and placebo in medically ill patients (6.7% with current or previous cancer) demonstrated lower rates of DVT with LMWH than with placebo [odds ratio (OR): 0.60; 95% CI: 0.47 to 0.75], but no difference when LMWH was compared with UFH (OR: 0.92; 95% CI: 0.56 to 1.52). The groups showed no differences in rates of death, VTE, or bleeding[44]. The EXCLAIM trial, which compared LMWH (enoxaparin) with placebo in 5963 acutely ill inpatients (1.6% cancer patients), showed a nonsignificant reduction (2.5% vs. 4.0%) in the rate of VTE events with LMWH. The rate of major bleeding was slightly higher with LMWH, but not statistically different from the rate with placebo[37]. However, the MEDENOX trial, which compared LMWH (enoxaparin) with placebo in 1102 hospitalized patients, showed a significant reduction in the incidence of VTE with LMWH (5.5% vs. 14.9%, $p < 0.001$)[45].

The LMWHs have not been compared head-to-head exclusively in cancer patients, but in other populations, no advantages in VTE incidence or bleeding rates were observed for any one agent[46–51]. Unfortunately, a need for cancer-specific DVT prophylaxis trials remains. Recommendations for DVT prophylaxis in cancer inpatients are typically extrapolated from non-cancer-specific DVT prophylaxis trials; only subgroup analyses of non-cancer specific trials are currently available. A meta-analysis by Carrier *et al.*[52] of all available data on cancer inpatients showed no significant reduction in the occurrence of VTE with either LMWH or fondaparinux prophylaxis [relative risk (RR): 0.91; 95% CI: 0.21 to 4.0]. Although DVT

prophylaxis is likely effective in cancer populations because of a higher rate of VTE, cancer-specific trials are necessary to help select appropriate patients and effective regimens of DVT prophylaxis.

4.3 Prophylaxis in Patients Undergoing Cancer Surgery

Consensus recommendations support VTE prophylaxis in patients undergoing major cancer surgery. That consensus is based on the increased risk of VTE in patients undergoing surgery that is at least 1 hour in length (Table I). Including a 2011 Cochrane meta-analysis of 16 RCTs with 11,847 patients[53], there are data, all relating to preoperative prophylactic anticoagulation, that show neither a beneficial nor a harmful effect of LMWH compared with UFH in terms of mortality, symptomatic DVT, pulmonary embolism, and minor or major bleeding. However, the analyses included data from patients enrolled in

TABLE II Guideline questions and recommendations related to the prophylaxis of venous thromboembolism (VTE)

Category	*Question*	*Recommendations*	*Strength of evidence*	
			Grade	*Consensus category*
Cancer patients				
Ambulatory	1.	Is prophylactic anticoagulant therapy recommended for all cancer outpatients?		
		Prophylactic anticoagulant therapy is not recommended for all outpatients with active malignancy.	1A	Immediate
	2.	Should cancer outpatients receiving chemotherapy receive prophylactic anticoagulation?		
		Outpatients with active malignancy receiving chemotherapy at high risk of thrombosis should be considered for prophylactic anticoagulant therapy.	2D	After discussion
Hospitalized	3.	Should cancer inpatients with acute illness or decreased mobility receive prophylactic anticoagulation?		
		Hospitalized patients with active malignancy and acute illness or decreased mobility should receive prophylactic anticoagulant therapy in the absence of contraindications.	1B	Immediate
	4.	Should cancer inpatients with no other risk factors receive prophylactic anticoagulation?		
		Hospitalized patients with active malignancy and no other risk factors should receive prophylactic anticoagulant therapy in the absence of contraindications.	2B	Immediate
	5.	Is low molecular weight heparin (LMWH) the prophylactic treatment of choice in cancer inpatients?		
		In hospitalized patients with cancer, LMWH is the treatment of choice.	1B	Immediate
Undergoing cancer surgery	6.	Is prophylactic anticoagulation recommended for cancer outpatients undergoing major cancer surgery?		
		Prophylactic anticoagulant therapy is recommended for outpatients undergoing major abdominal or pelvic cancer surgery.	1A	Immediate
	7.	Is extended prophylactic anticoagulation recommended for cancer outpatients after major surgery?		
		Extended prophylaxis for deep vein thrombosis (DVT) should be considered for up to 4 weeks postoperatively in patients undergoing major abdominal or pelvic cancer surgery, especially in those at high risk. Although there appears to be benefit, the associated risk (bleeding) is not clear.	2B	After discussion
	8.	Should cancer outpatients undergoing low-risk surgeries be considered for anticoagulation?		
		The evidence is insufficient to recommend prophylactic anticoagulation in outpatients undergoing lower-risk surgeries (that is, biopsies, cutaneous excisions, and so on)	5D	After discussion
With advanced cancer	9.	Should cancer patients who have completed active therapy but who have stable metastases continue anticoagulation?		
		Patients who have completed active therapy but who have stable metastases should continue anticoagulant therapy beyond the initial 6 months.	5D	Immediate
	10.	Should patients for whom cancer therapy has been withdrawn continue anticoagulation?		
		Once cancer therapy is withdrawn, the risks, discomfort, and inconvenience of taking anticoagulant therapy should be re-weighed against the benefits of preventing recurrent VTE.	5D	Immediate

TABLE II Continued

Category	*Question*	*Recommendations*	*Strength of evidence*	
			Grade	*Consensus category*
With special clinical scenarios	11.	Should cancer outpatients with a central venous catheter (CVC) and no other risk factors receive prophylactic anticoagulation?		
		A CVC alone is not an indication for prophylactic anticoagulation therapy in outpatients with active malignancy.	1B	Immediate
	12.	Are there special considerations for elderly patients receiving prophylactic anticoagulant therapy?		
		Elderly patients more than 70 years of age with reduced creatinine clearance could be at greater risk of LMWH-induced complications such as bleeding.	4D	Immediate
	13.	Is there a preferred prophylactic anticoagulant therapy for elderly patients with active malignancy?		
		There is no high-level evidence to recommend one LMWH or unfractionated heparin (UFH) over another in elderly patients with active malignancy.	2B	After discussion
	14.	Is there a preferred prophylactic anticoagulant therapy for patients with impaired renal function?		
		There is no high level evidence to recommend one LMWH or UFH over another in patients with impaired renal function. Enoxaparin might have a less favourable biologic profile than tinzaparin and dalteparin in patients with impaired renal function.	2B	Immediate
	15.	Should patients with persistent or severe thrombocytopenia receive prophylactic anticoagulation?		
		Patients with persistent or severe thrombocytopenia should be referred to a hematologist or thrombosis expert where possible.	5D	After discussion
		In patients with significant thrombocytopenia, LMWH or UFH is preferred over vitamin K agonists if anticoagulation is necessary.	5D	After discussion
	16.	Can prophylactic anticoagulant therapy be used in patients with central nervous system malignancy with VTE?		
		Anticoagulant therapy can be used in patients with central nervous system malignancy.	4D	Immediate
	17.	Are there special considerations for the administration of prophylactic anticoagulation in obese cancer patients?		
		Administration of LMWH should be based on actual body weight rather than ideal body weight.	2C	Immediate
Prophylactic therapy				
Preferred type	18.	What is the preferred LMWH for VTE prophylaxis in the cancer outpatient setting?		
		There is no preferred LMWH for VTE prophylaxis in cancer outpatients; the choice of anticoagulant is at the discretion of the treating physician.	5D	After discussion
	19.	Can direct oral anticoagulant agents (that is, apixaban, dabigatran, rivaroxaban) be used for the prophylaxis of cancer-associated thrombosis?		
		Direct oral anticoagulant agents (that is, apixaban, dabigatran, rivaroxaban) have not yet been proved to be efficacious or safe in oncology patients and are currently not recommended for the prophylaxis of cancer-associated thrombosis.	2C	Immediate
To improve overall survival	20.	Should anticoagulant therapy be used to prolong survival in cancer patients without the presence of risk factors for VTE?		
		The use of adjuvant anticoagulant therapy in patients without established VTE or unselected (low-risk) patients to prolong survival is not recommended.	2B	Immediate
Monitoring	21.	Should levels of anti–factor Xa be monitored in patients receiving prophylactic anticoagulation?		
		Monitoring of anti–factor Xa is generally not recommended in most patients receiving prophylactic anticoagulation.	1A	Immediate
	22.	Should levels of anti–factor Xa be monitored in patients with renal insufficiency receiving prophylactic anticoagulation?		
		Anti–factor Xa could be checked at baseline and periodically in patients with renal insufficiency at the discretion of the treating physician, with clinical correlation.	5C	After discussion

TABLE III Predictive model for chemotherapy-associated venous thromboembolism[4]

Patient characteristic	*Risk score*[a]
Site of cancer	
Very high risk (cancers of the stomach, pancreas, and brain)	2
High risk (cancers of the lung, bladder, and testes; lymphoma; gynecologic malignancies)	1
Pre-chemotherapy platelet count ≥ 350,000/μL	1
Hemoglobin < 10 g/dL or use red blood cell growth factors	1
Pre-chemotherapy leucocyte count > 11,000/μL	1
Body mass index ≥ 35 kg/m^2	1

[a] A score of 3 or greater is indicative of a 7% risk (for example, high risk); a score of 1–2 is indicative of a 2% risk; a score of 0 is indicative of a 0.5% risk.

non-cancer-specific trials and were based largely on older data using positive screening radiologic imaging events as an endpoint. The CANBESURE trial, published in 2010, compared bemiparin with placebo in 625 cancer surgery patients and found that the rate of VTE was significantly less in patients treated with bemiparin (0.8% vs. 4.6%, $p = 0.01$)[29]. The use of anticoagulation in patients undergoing major cancer surgery has been endorsed elsewhere[14].

Current guidelines recommend extending postoperative prophylaxis for up to 4 weeks in patients undergoing abdominal or pelvic cancer surgery[14–18]. A meta-analysis comparing the extended use of LMWH (3–4 weeks after surgery) with conventional in-hospital prophylaxis (for the period of time in hospital) evaluated data from patients undergoing major abdominal surgery. The analyzed trials showed that extended prophylaxis significantly reduced the incidence of VTE (RR: 0.44; 95% CI: 0.28 to 0.70; $p < 0.05$), DVT (RR: 0.46; 95% CI: 0.29 to 0.74; $p < 0.05$), and proximal DVT (RR: 0.24; 95% CI: 0.09 to 0.67; $p < 0.05$), with no significant differences in major or minor bleeding[54]. Using data from four trials, a Cochrane meta-analysis comparing prolonged LMWH thromboprophylaxis with control treatment or placebo showed that prolonged thromboprophylaxis with LMWH was associated with a 78% lower risk of developing symptomatic VTE (OR: 0.22; 95% CI: 0.06 to 0.80; $p = 0.02$)[55]. In both meta-analyses, the trials were non-cancer-specific, and the primary endpoint was positive radiologic screening, with only a few symptomatic events noted.

Currently, only limited data are available from investigations of the role of anticoagulant therapy in patients undergoing low-risk cancer surgery. Risk factors for VTE in patients undergoing outpatient surgery include an operative time greater than 120 minutes (OR: 1.69; $p = 0.027$), arthroscopic surgery (OR: 5.16; $p < 0.001$), saphenofemoral junction surgery (OR: 13.20; $p < 0.001$), and venous surgery not involving the great saphenous vein (OR: 15.61; $p < 0.001$)[56]. However, data on the use of anticoagulation in those patients are lacking.

4.4 Preferred Prophylactic Therapy

The preferred anticoagulation therapy in the prophylactic setting is LMWH. There are no clinical data comparing tinzaparin, enoxaparin, and dalteparin in the prophylactic setting in patients with active malignancy, patients undergoing non-orthopedic surgery, or acutely ill patients. Based on data from hospitalized non-cancer patients indicating similar efficacy and bleeding rates[47–50], it is reasonable to suggest that no particular LMWH is superior to another in that setting. Dalteparin is typically dosed subcutaneously at 5000 U daily[25,27]. Enoxaparin is typically dosed subcutaneously at 40 mg daily or, in patients with severe renal impairment, at 30 mg daily[35,37,38,57]. Tinzaparin is typically dosed subcutaneously at 4500 U daily or 75 U/kg daily[58].

4.5 Prophylaxis in Special Clinical Scenarios

4.5.1 Patients with a Central Venous Catheter

The role of anticoagulation in the prevention of central venous catheter (CVC)–related thrombosis has been investigated[39,59]. Although anticoagulants have been shown not to increase the risk of bleeding, three systematic reviews and a meta-analysis failed to show that they lower the incidence of symptomatic CVC-related thrombosis[60–63]. Thromboprophylaxis for a CVC is therefore not recommended[14–17].

4.5.2 Patients with Renal Insufficiency

In patients with impaired renal function (creatinine clearance ≤ 30 mL/min), LMWH can accumulate as a result of reduced excretion, which could result in an increased risk of bleeding. Prophylactic LMWH should therefore be used with caution in patients with renal impairment[64]. Tinzaparin has the highest average molecular weight (6500 Da) of the available LMWHs, followed by dalteparin (6000 Da). Enoxaparin (4500 Da) is the smallest and most renal-dependent LMWH. In contrast, by virtue of its larger size, tinzaparin appears to be less dependent on renal clearance and more dependent on the reticuloendothelial system[65]. Tinzaparin might therefore be preferable in patients with renal insufficiency.

4.5.3 Elderly Patients

There are limited data and no RCTs comparing tinzaparin, enoxaparin, and dalteparin with each other or with UFH or coumadin in elderly patients with cancer. The DIRECT study included critically ill patients ($n = 138$) with a creatinine clearance less than 30 mL/min given dalteparin (5000 IU daily) in the prophylactic setting. Bioaccumulation (that is, a factor Xa

level > 0.40 IU/mL) was observed in no patients (0%; 95% CI: 0% to 3.0%) and the median trough level of factor Xa was below the detectable limit (<0.10 IU/mL)[66]. A RCT that enrolled patients with a median creatinine clearance of 34.7 ± 11.4 mL/min randomized to enoxaparin (40 mg) or to tinzaparin once daily in the prophylactic setting found that factor Xa did not accumulate significantly for tinzaparin, but did accumulate for enoxaparin ($p < 0.0001$)[67]. None of the available data are cancer-specific.

4.5.4 Patients with Thrombocytopenia

No trials have evaluated bleeding risk relative to platelet count in any population of patients requiring prophylactic anticoagulation. In general, thrombocytopenic patients are excluded from anticoagulation trials. Expert opinion would suggest that the bleeding risk is negligible in patients with an isolated thrombocytopenia when platelets number 50,000/μL or more; however, spontaneous bleeding, including fatal intracranial hemorrhage, is typically felt to be more relevant in patients with a platelet count below 20,000/μL. The American Society of Clinical Oncology guidelines do not recommend prophylaxis with anticoagulants in patients with a platelet count below 50,000/μL[14], but many experts in the field suggest that prophylactic anticoagulation can rationally be used for specific patients with platelet counts as low as 20,000/μL[68–70]. In such situations, we recommend consultation with thrombosis experts.

4.5.5 Patients with Central Nervous System Malignancy

Anticoagulation is acceptable in patients with central nervous system malignancies, but should be provided at the discretion of the treating physician. The PRODIGE trial randomized 186 adults with malignant glioma to subcutaneous dalteparin (5000 U) or to placebo once daily and reported no difference in the incidence of VTE in the first 6 months (9.1% vs. 14.9% respectively; hazard ratio: 0.51; 95% CI: 0.19 to 1.4; $p = 0.29$). Major bleeding at 12 months was also not significantly different (5.1% vs. 1.2%, $p = 0.22$)[25]. A retrospective series of 40 newly diagnosed patients with grade 3 or 4 malignant glioma initiated on a prophylactic dose of daily tinzaparin between 48 hours and 4 weeks postoperatively for a planned duration of 12 months reported grade 4 or 5 central nervous system hemorrhages or grade 2 or greater systemic hemorrhages. Of the 40 patients, 1 developed a DVT while taking tinzaparin, and 3 developed thromboembolic complications while off tinzaparin[58]. Similar findings from retrospective reviews of bleeding events have been reported elsewhere in patients with central nervous system malignancy receiving prophylactic anticoagulation[71,72].

4.5.6 Obese Patients

Patients with a body mass index greater than 30 kg/m^2 are considered to be obese[73], and the anticoagulation needs of most patients in that range will exceed the highest prefilled syringes of LMWH. A prospective comparison of three enoxaparin dosing regimens for DVT prophylaxis in 531 medically ill patients with extreme obesity (>40 kg/m^2) showed that peak factor Xa levels were significantly higher in the higher weight-based dose group (enoxaparin 0.5 mg/kg daily) than in the lower weight-based dose group (enoxaparin 0.4 mg/kg daily) or in the fixed-dose group (40 mg daily). Compared with the lower weight-based dose or fixed-dose groups, the higher weight-based dose group more frequently achieved target factor Xa levels ($p < 0.05$). No adverse event (bleeding, thrombosis) occurred in any group[74].

Weight-adjusted tinzaparin and dalteparin dosing showed a predictable response regardless of body weight or body mass index, without a need for maximal absolute dose capping[75,76]. Given that no available data suggest increased bleeding rates or other toxicities at higher LMWH doses in obese patients, the consensus recommendation is to avoid dose-capping or the use of ideal body weight for dose calculations; for all LMWHs, use the actual weight-based dose.

4.6 New Oral Anticoagulants

Novel direct oral anticoagulants that have been developed include factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and thrombin inhibitors (dabigatran). Some of these agents have completed phase III trials in DVT prophylaxis after hip and knee replacement surgery and for medically ill patients[77–79]. However, data for cancer-specific populations in those studies are lacking. Data are limited mostly to *post hoc* analyses of subgroups, which typically constituted only about 5% of the total study population. In addition, variable definitions of cancer were used in each trial, many of which did not reflect accepted definitions of active cancer.

Cancer subgroups from the DVT prophylaxis trials showed a concerning trend toward no efficacy, but increased rates of major bleeding. Compared with a parenteral agent, oral agents could be disadvantaged in patients at increased risk of gastrointestinal dysfunction (because of nausea, vomiting, and so on), altered absorption patterns, and drug interactions. All of those limitations highlight the need for more high-quality cancer-specific clinical trials before novel direct oral anticoagulants can be endorsed. Use of such agents is not recommended for cancer-associated thromboprophylaxis.

4.7 Anticoagulation to Improve Overall Survival

It is not recommended that anticoagulation be used to extend survival in patients with cancer in the absence of other indications for anticoagulation[14]. However, there are interesting data to suggest that a survival benefit might accrue to the use of LMWH in cancer

patients. A meta-analysis of 3343 patients from eleven studies of UFH (one trial), LMWH (six trials), and warfarin (four trials) compared anticoagulation treatment with no anticoagulation or placebo for primary VTE prophylaxis. The results showed a lower risk of mortality that was statistically significant for LMWH ($p = 0.015$), but not for UFH ($p = 0.095$) or warfarin ($p = 0.239$). With all anticoagulant options, the rate of major bleeding was observed to be increased ($p < 0.0001$), although the increase was not significant for LMWH on its own ($p = 0.128$)[80]. Notably, more than half the included trials had been published more than 15 years earlier.

Two Cochrane reviews of clinical trials assessed cancer survival with the addition of oral anticoagulation (six trials with warfarin, one trial with apixaban)[81] or parenteral anticoagulation (one trial with UFH, eight trials with LMWH; 2857 participants in total)[82] compared with no anticoagulation or placebo. At 1 year, no mortality benefit was observed for UFH and LMWH; however, at 2 years, a statistically significant mortality benefit emerged (RR: 0.79; 95% CI: 0.67 to 0.93). Major bleeding was increased (RR: 1.30; 95% CI: 0.59 to 2.88), and the difference was statistically significant. Despite those interesting observations, many of the available studies were published more than 15 years ago, included small numbers of patients or represented subgroup or *post hoc* analyses, or did not focus on survival as the primary outcome. The cancer types studied were also limited, and so results might not apply broadly. Finally, major bleeding rates were uniformly elevated. Until more rigorous randomized trials using modern cancer therapies and anticoagulation regimens are conducted in future, anticoagulation to extend survival in patients with cancer is not recommended[83].

5. SUMMARY

This is the first national Canadian guideline on the prophylaxis of VTE in cancer patients. Patients with cancer are at increased risk of VTE. Prophylactic antithrombotic therapy with LMWH can greatly reduce the risk of VTE, particularly for hospitalized cancer patients. Some subgroups of patients with cancer, including those with thrombocytopenia, renal insufficiency, and obesity might require modifications of the anticoagulant regimen. Use of direct oral anticoagulants for prophylaxis is not supported at the present time.

6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: JCE has received honoraria from Leo Pharma, Sanofi, and Pfizer. CMJW has received honoraria from Leo Pharma and Pfizer. PK has received educational grants from Sanofi and Leo Pharma and has also served on the Leo Pharma advisory board. SS has received honoraria from Leo Pharma and Pfizer. VT has received honoraria and unrestricted grants from Sanofi and Pfizer. HJL has received honoraria from Sanofi. No other author had a conflict to declare.

8. REFERENCES

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Correspondence to: Jacob Easaw, Department of Oncology, Tom Baker Cancer Centre, 1331 29th Street NW, Calgary, Alberta T2N 4N2; or Petr Kavan, Department of Oncology, Jewish General Hospital, 3755 Côte-Sainte-Catherine Road, Montreal, Quebec H3T 1E2.
E-mail: jay.easaw@albertahealthservices.ca or petr.kavan@mcgill.ca

* Alberta: Department of Oncology, Cumming School of Medicine, University of Calgary, Tom Baker Cancer Centre, Calgary (Easaw, Shea–Budgell); Cancer Strategic Clinical Network, Alberta Health Services, Calgary (Shea–Budgell); Division of Hematology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton (Wu); Guideline Utilization Resource Unit, CancerControl Alberta, Alberta Health Services, Calgary (Meek).
† Manitoba: Department of Medicine, University of Manitoba, Cancer Care Manitoba, Winnipeg (Czaykowski).
‡ Quebec: Hôpital Maisonneuve–Rosemont, Montreal (Kassis); Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal (Tagalakis); Department of Oncology, Faculty of Medicine, McGill University, Montreal (Kavan).
§ Ontario: Scientific Insights Consulting Group, Mississauga (Kuehl); Department of Medicine, St. Michael's Hospital Division of Nephrology, University of Toronto, Toronto (McFarlane); Department of Oncology, Western University, London (Welch).
‖ British Columbia: Department of Medical Oncology, BC Cancer Agency, Vancouver (Lim); BC Provincial Renal Agency and Faculty of Pharmaceutical Sciences, University of British Columbia and Royal Jubilee Hospital, Victoria (Martinusen).
Nova Scotia: Department of Medicine, Dalhousie University, Halifax (MacNeil); Department of Medicine, Dalhousie University and Capital District Health Authority, Halifax (Shivakumar).
** Saskatchewan: Department of Medicine, Division of Hematology, University of Saskatchewan, Saskatoon (Moodley).