Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment

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ABSTRACT

Patients with cancer are at increased risk of venous thromboembolism (VTE). Anticoagulation therapy is used to treat VTE; however, patients with cancer have unique clinical circumstances that can often make decisions surrounding the administration of therapeutic anticoagulation complicated. No national Canadian guidelines on the management of established 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 is the treatment of choice for cancer patients with established VTE. Direct oral anticoagulants are not recommended for the treatment of VTE at this time. Specific clinical scenarios, including the presence of an indwelling venous catheter, renal insufficiency, and thrombocytopenia, warrant modifications in the therapeutic administration of anticoagulation therapy. Patients with recurrent VTE should receive extended (>3 months) anticoagulant therapy. Incidental VTE should generally be treated in the same manner as symptomatic VTE. There is no evidence to support the monitoring of anti-factor Xa levels in clinically stable cancer patients receiving prophylactic anticoagulation; however, levels of anti-factor Xa could be checked at baseline and periodically thereafter in patients with renal insufficiency. Follow-up and education about the signs and symptoms of VTE are important components of ongoing patient care.

KEY WORDS

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

1. INTRODUCTION

Complex cancer treatments and the presence of comorbidities can complicate the treatment of venous thromboembolism (VTE) in patients with cancer. Guidelines on the management of VTE in the oncology setting have been developed by the American Society of Clinical Oncology¹ and CancerControl Alberta (part of Alberta Health Services)², but fail to address several key issues concerning the monitoring of anticoagulation and the use of anticoagulants in specific subpopulations. Other guidelines are broader in scope, and their discussion of treatment for VTE is therefore limited to a subsection^{3–5}. No national guidelines specifically focus on the treatment of cancer-associated VTE. We therefore aimed to develop national recommendations that are evidence-based (or consensus-based where evidence is lacking) on the treatment of VTE in cancer patients.

The resulting recommendations provide guidance to physicians, nurses, and other frontline medical professionals involved in the management of patients with cancer. The recommendations address the preferred therapy and dosing for established VTE; duration of therapy; management of incidental VTE, of VTE related to a central venous catheter (CVC), and of established VTE in special clinical scenarios; patient education; and the monitoring of anticoagulation therapy.

2. METHODOLOGY

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 treatment 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 Excellence⁶, the *Archives of Pediatrics and Adolescent Medicine*⁷, and the AGREE collaboration⁸. Clinical questions and initial recommendations were developed by two medical oncologists (JCE and PK) and a cancer research methodologist (MAS), based on the literature review and clinical experience treating patients with cancer and VTE. The University of Oxford Centre for Evidence-Based Medicine grading system was used to grade the recommendations⁹.

The resulting 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 a working group 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 fifty-six publications, including three clinical practice guidelines. Meta-analyses and RCTs were considered to be strong or higher-level evidence in developing the recommendations. Several relevant retrospective case series were also included in the discussion, but were considered to be weak or lower-level evidence. Based on the Web survey responses, consensus was reached immediately on 25 of the 34 final recommendation statements (74%). The remaining 9 recommendations were further discussed by the assigned panel members to reach consensus. Consensus was eventually reached for all 34 recommendation statements (Table 1).

4. DISCUSSION

4.1 Therapy Types and Dosing for the Treatment of Established VTE

4.1.1 Low Molecular Weight Heparin

For cancer patients on active treatment who develop VTE, therapy with low molecular weight heparin (LMWH) is more effective than therapy with warfarin in preventing recurrent blood clots¹⁰. The CLOT trial—which included 672 cancer patients with acute symptomatic proximal DVT, pulmonary embolism (PE), or both—compared LMWH with warfarin. All patients were initially treated for 6 months with either subcutaneous dalteparin (200 IU/kg daily for 1 month, followed by 150 IU/kg daily for 5 months) or warfarin [bridged with LMWH until the patient’s international normalized ratio (INR) reached 2–3]. Recurrent VTE occurred in 8% of the dalteparin group and in 16% of the warfarin group [hazard ratio (HR): 0.48; $p = 0.002$]. The groups did not differ in their rates of major bleeding and any bleeding (6% vs. 4% and 14% vs. 19% respectively)¹¹.

Data from the CATCH RCT, which compared tinzaparin 175 IU/kg once daily for 6 months or initial tinzaparin 175 IU/kg once daily overlapped and followed by dose-adjusted warfarin (target INR: 2.0–3.0) for 6 months in cancer patients with symptomatic VTE, demonstrated lower rates of recurrent VTE with tinzaparin [HR: 0.65; 95% confidence interval (CI): 0.41 to 1.03; $p = 0.07$]; however, that difference was not statistically significant. Clinically relevant non-major bleeding was lower with tinzaparin than with warfarin [50 patients (11%) and 73 patients (16%) respectively, $p = 0.03$]¹². Importantly, CATCH (conducted more than a decade after the CLOT study) showed that tinzaparin use was associated with clot recurrence at rates similar to those seen with other LMWHs, but that the clot recurrence rate for warfarin-treated patients was less frequent than expected. One possible explanation for those findings is that physicians or anticoagulation monitoring services (or both) are doing a more effective job of preventing

CANADIAN RECOMMENDATIONS FOR VTE TREATMENT IN CANCER

TABLE 1 Guideline questions and recommendations related to the treatment of venous thromboembolism (VTE)

Category	Question	Recommendations	Strength of evidence	
			Grade	Consensus category
Preferred therapy and dosing	1. Is there a preferred anticoagulation therapy for cancer patients with established VTE?	In patients with established VTE, low molecular weight heparin (LMWH) is the treatment of choice because of decreased recurrence rates on treatment.	1A	Immediate
	2. When should warfarin be used in cancer patients with established VTE?	Warfarin (INR 2–3), although less favoured, can be used in situations in which LMWH is contraindicated or the patient refuses LMWH.	1A	Immediate
	3. Can direct oral anticoagulation agents (that is, apixaban, dabigatran, rivaroxaban) be used for the treatment 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 treatment of cancer-associated thrombosis.	2C	Immediate
	4. What is the appropriate dosing for dalteparin in cancer patients with VTE?	For cancer-associated VTE, dalteparin is used subcutaneously at 200 U/kg daily for the first month, followed by 150 U/kg daily for the subsequent 5 months.	1A	After discussion
		The evidence is insufficient to support subcutaneous dosing of dalteparin at 200 U/kg daily without dose reduction; however, this regimen is used in clinical practice.	5D	After discussion
	5. What is the appropriate dosing for enoxaparin in cancer patients with VTE?	There is evidence to support subcutaneous dosing of enoxaparin at 1 mg/kg twice daily or 1.5 mg/kg once daily in the general population, but cancer-specific data are limited.	2B	After discussion
		Consider using the twice-daily dosing regimen in high-risk populations such as those with cancer.	5D	After discussion
	6. What is the appropriate dosing for tinzaparin in cancer patients with VTE?	Tinzaparin should be dosed at 175 U/kg daily subcutaneously.	1A	Immediate
Duration of therapy	7. Should patients with recurrent VTE while receiving therapeutic anticoagulation receive a dose increase? If so, by how much?	Patients with recurrent VTE while on LMWH should receive a dose increase of 20%–25%.	4D	Immediate
	8. Are there special considerations for the administration of anticoagulation therapy in obese cancer patients with established VTE?	Administration of LMWH should be based on actual body weight rather than on ideal body weight. Dose capping is not recommended.	2C	Immediate
	9. Should anticoagulant therapy be extended in patients with recurrent VTE?	Patients with recurrent VTE should receive extended (>3 months) anticoagulation therapy.	2B	Immediate
Incidental VTE	10. How should incidental VTE be managed in cancer patients?	Incidental VTE should generally be treated in the same manner as symptomatic VTE; however, dosing in proximal deep vein thrombosis (DVT) and pulmonary embolism (PE) has not been studied.	4D	Immediate
Central venous catheter–related VTE	11. Should cancer patients with upper-extremity DVT in whom the central venous catheter (CVC) has not been removed receive anticoagulation therapy?	Anticoagulation therapy for the duration of the CVC is recommended for cancer patients with upper-extremity DVT in whom the CVC has not been removed.	1A	Immediate
	12. How long should cancer patients with upper-extremity DVT and CVC removal receive anticoagulation?	Anticoagulation therapy for at least 3 months is recommended for cancer patients with upper-extremity DVT in whom the CVC has been removed.	1B	Immediate

TABLE 1 Continued

Category	Question	Recommendations	Strength of evidence	
			Grade	Consensus category
Inferior vena cava filter	13. Should an inferior vena cava (IVC) filter be used in combination with anticoagulation therapy in cancer? The addition of an IVC filter to anticoagulation therapy is not recommended; however, in patients with an IVC filter, anticoagulation therapy can be used in the absence of contraindications.		1B	Immediate
Patients with renal insufficiency	14. Are there special considerations for elderly patients with cancer receiving anticoagulation therapy for established VTE? 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
	15. Is there a preferred anticoagulation therapy for elderly cancer patients with established VTE? There is no high level evidence to recommend one LMWH or unfractionated heparin (UFH) over another in elderly patients with active malignancy. Tinzaparin might have a favourable biologic profile using therapeutic dosing in the setting of renal insufficiency.		2B	After discussion
	16. Is there a preferred anticoagulation therapy for cancer patients with impaired renal function with established VTE? 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
	17. Can cancer patients with established VTE undergoing hemodialysis receive LMWH? In patients with active malignancy who are undergoing hemodialysis, LMWH should not routinely be used and should be administered only after consultation with a nephrologist.		3C	After discussion
Patients with low platelet counts	18. Should cancer patients with persistent or severe thrombocytopenia receive anticoagulation therapy for established VTE? Patients with persistent or severe thrombocytopenia should be referred to a hematologist or thrombosis expert where possible. In patients with significant thrombocytopenia, LMWH or UFH is preferred over vitamin K agonist if anticoagulation is necessary.		5D	After discussion
			5D	After discussion
	19. Should cancer patients with a platelet count below 20,000/ μ L receive anticoagulation for established VTE? For acute clot (<1 month) in patients with platelet counts below 20,000/ μ L, hold anticoagulation unless platelet transfusion support is available to maintain a platelet count of at least 50,000/ μ L. For chronic or subacute VTE ($\geq$ 1 month) in patients with platelet counts below 20,000/ μ L, hold anticoagulation.		5D	After discussion
			5D	After discussion
	20. Should cancer patients with a platelet count of 20,000–50,000/ μ L receive anticoagulation for established VTE? For acute clot (<1 month) in patients with platelet counts of 20,000–50,000/ μ L, consider full-dose anticoagulation if the patient can be supported with platelet transfusions. For chronic or subacute VTE ($\geq$ 1 month) in patients with platelet counts of 20,000–50,000/ μ L, use dose-reduced LMWH.		5D	After discussion
			5D	After discussion
Cirrhosis	21. Should cancer patients with a platelet count of 50,000–100,000/ μ L receive anticoagulation for established VTE? Patients with a platelet count of 50,000–100,000/ μ L can receive anticoagulation without the need for dose reductions unless the risk of bleeding is high.		2B	Immediate
	22. Can prophylactic LMWH be used in patients with liver disease? In patients with liver disease, LMWH can be used.		2C	Immediate

TABLE 1 Continued

Category	Question	Recommendations	Strength of evidence	
			Grade	Consensus category
Monitoring	23. Should levels of anti-factor Xa be monitored in cancer patients undergoing anticoagulation therapy for established VTE?	Monitoring of anti-factor Xa is generally not recommended for most patients.	1A	Immediate
	24. Should levels of anti-factor Xa be monitored in cancer patients with renal insufficiency undergoing anticoagulation therapy for established VTE?	There is no evidence to support the monitoring of anti-factor Xa in uncomplicated patients receiving therapeutic anticoagulation.	2B	After discussion
		Anti-factor Xa could be checked at baseline and periodically in selected patients (that is, patients who experience recurrent clot despite receiving therapeutic anticoagulation, and patients with renal insufficiency) at the discretion of the treating physician. In patients with renal insufficiency, clinical correlation is recommended.	5C	After discussion
	25. What is the optimal therapeutic range for anti-factor Xa in patients with cancer?	The optimal therapeutic range for anti-factor Xa has not been established; however, the generally accepted ranges for treatment are 0.5–1.1 U/mL for twice-daily dosing and 1.0–2.0 U/mL for daily dosing.	4D	Immediate
	26. Should cancer patients for whom the risk of heparin-induced thrombocytopenia (HIT) is high undergo platelet monitoring?	In the outpatient setting, any patient receiving LMWH should undergo platelet monitoring at baseline and at one other point between days 5 and 14.	5D	After discussion
	27. How should strongly suspected or confirmed HIT, whether complicated by thrombosis or not, be treated in patients with cancer?	Strongly suspected or confirmed HIT, whether complicated by thrombosis or not, should be treated with a non-heparin agent. Health Canada–approved agents include lepirudin, argatroban, and danaparoid. Off-label agents include bivalirudin and fondaparinux.	1A	Immediate
	28. Should warfarin be used to treat strongly suspected or confirmed HIT in patients with cancer? If so, when?	Strongly suspected or confirmed HIT should not be treated with warfarin until after the platelet count has substantially recovered ($\geq 150,000/\mu\text{L}$).	1A	Immediate
	29. What baseline measurements should be performed to ensure that anticoagulation is safe in patients with cancer?	A baseline complete blood count, creatinine, liver function tests, and INR or partial thromboplastin time are recommended to rule out severe thrombocytopenia, renal or hepatic impairment and coagulopathy.	5D	Immediate
	30. When should patients receiving anticoagulant therapy be followed up?	An initial follow-up should occur at 1–4 weeks.	5D	Immediate
	31. What should be assessed during follow-up visits?	Follow-up visits should ensure that subcutaneous injections are being administered properly and should assess for bleeding and recurrent thrombotic complications.	5D	Immediate
Patient education	32. How should patients be educated about their condition, including their personal risk for recurrence?	Patients should be given verbal and written education about their condition, including their personal risk for developing recurrent VTE.	5D	Immediate
	33. How should patients be educated about monitoring and surveillance?	Patients should be informed of the signs and symptoms of DVT and PE and what to do if either condition is suspected.	5D	Immediate
	34. How should patients be educated about their planned therapy?	Patients should be given verbal and written education about their planned therapy, including possible side effects (namely bleeding) and restrictions (that is, avoidance of aspirin, alcohol in moderation only, and so on), and should be instructed to inform other health care providers that they are using anticoagulation therapy.	5D	Immediate

INR = international normalized ratio.

warfarin-associated clot recurrence than had previously been seen.

Similarly, the LITE trial¹³ compared tinzaparin and warfarin in a subgroup of 200 cancer patients with acute symptomatic proximal DVT and found, after 12 months of follow-up, recurrent VTE in 7% of the tinzaparin group and in 16% of the vitamin K antagonist group (relative risk: 0.44; $p = 0.044$). Bleeding did not differ between the groups (27% vs. 24%).

No phase III trials for enoxaparin have been completed. The CANTHANOX trial comparing subcutaneous enoxaparin (1.5 mg/kg once daily) and warfarin for 3 months in 146 cancer patients with VTE showed that the rate of recurrent VTE was not statistically different between the groups: 21.1% (95% CI: 12.3 to 32.4) for warfarin versus 10.5% (95% CI: 4.3 to 20.3) for enoxaparin ($p = 0.09$)¹⁴. However, the study was stopped early because of poor accrual.

Lastly, the ONCENOX trial evaluated 6 months of enoxaparin alone compared with initial enoxaparin followed by warfarin for the secondary prevention of VTE in 122 cancer patients with acute symptomatic VTE. The trial was stopped early, but found significant differences in the rates of major and minor bleeding between the treatment groups¹⁵.

Dosing for enoxaparin is based on a large phase III trial in 900 patients ($n = 141$, 15.7% with cancer) with symptomatic lower-extremity DVT, which found that recurrent VTE occurred in 3 of 45 patients (6.7%) in the UFH group, in 6 of 49 patients (12.2%) in the once-daily enoxaparin group, and in 3 of 47 patients (6.4%) in the twice-daily enoxaparin group. Major hemorrhage did not differ between the groups (2.1% UFH vs. 1.7% once-daily enoxaparin vs. 1.3% twice-daily enoxaparin)¹⁶. Notably, the definition of cancer used in the trial was not provided, but the defined cancer patients were evenly distributed between the treatment groups. Although the numbers are small and the trial did not target cancer patients, the trend suggests that, in high-risk populations such as cancer patients, daily dosing of enoxaparin should be used with caution. Twice-daily dosing of enoxaparin might therefore be preferable¹⁶.

No cancer-specific RCTs have compared once-daily with twice-daily dosing of enoxaparin. Recommended dosing for subcutaneous dalteparin (200 U/kg daily for the first month, followed by 150 U/kg daily for the subsequent 5 months) and for subcutaneous tinzaparin (175 U/kg daily) are based on the CLOT¹¹ and LITE¹² trials respectively. Subcutaneous dosing of dalteparin at 200 U/kg daily without dose reduction has been used in clinical practice¹⁷.

4.1.2 Dosing in the Obese Patient

Patients with a body mass index greater than 30 kg/m² are considered to be obese¹⁸ and require actual weight-adjusted dosing, without a need for maximal absolute dose capping. Studies evaluating single doses of prophylactic or therapeutic tinzaparin¹⁹

and dalteparin²⁰ based on actual weight rather than ideal weight have demonstrated no additional risk of bleeding with dosing based on actual weight. Because 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 and to use all LMWHs at doses based on actual weight. It is also important to consider the higher thrombotic risk in cancer patients and the potential danger of underdosing in this population, which could result in increased rates of recurrent VTE.

4.1.3 Direct Oral Anticoagulants

Several novel direct oral anticoagulants—including factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and thrombin inhibitors (dabigatran)—have been developed. Those agents have all completed phase III trials in stroke prevention for nonvalvular atrial fibrillation, acute treatment, and secondary prevention of VTE^{21–24}, and some have completed phase III trials in DVT prophylaxis after hip and knee replacement surgery and for medically ill patients^{22,25,26}. However, data looking at cancer-specific populations in those studies²⁷ are sparse and mostly limited to *post hoc* analyses of subgroups, which typically comprised 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 active cancer definitions. Cancer subgroups from the DVT prophylaxis trials showed a concerning trend toward no efficacy, but increased rates of major bleeding. Cancer subgroups from the VTE treatment trials at best showed efficacy and safety similar to that seen with warfarin. In patients with active cancer, LMWH is superior to warfarin. Finally, oral agents might be disadvantaged compared with a parenteral agent for patients at increased risk of gastrointestinal dysfunction (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 the novel oral anticoagulants can be endorsed. Use of the novel agents is not recommended at this time in cancer-associated thrombosis.

4.2 Advanced Cancer and Duration of Therapy

A systematic review of data from nineteen cancer-specific studies, including randomized trials and cohort studies that included patients with advanced cancer, found that long-term full-dose LMWH is more effective than warfarin in the treatment of VTE. The review concluded that warfarin should not be used in patients with advancing progressive disease²⁸. The prothrombotic tendency of patients with advanced cancer suggests a need for indefinite treatment^{28–31}. Currently, randomized clinical data support the use of LMWH treatment for 3–6 months^{11,12}. In general, for patients treated with curative intent, LMWH treatment

is often given for 6 months. Extended antithrombotic therapy (beyond 6 months) is controversial, but is often used for patients with metastatic disease who will be treated with chemotherapy for prolonged periods of time. The suggestion that the extended use of LMWH is safe was tested in the DALTECAN study, which evaluated dalteparin for the long-term management (>6 months) of newly diagnosed VTE in cancer patients. Although presented only in abstract form, the resulting data suggested that, compared with the initial period of therapy, extended therapy is not associated with increased bleeding. Importantly, the risk for a recurrent blood clot was noted to be highest in the first month after dalteparin initiation³². Thereafter, the rate of subsequent VTE remained stable at nearly 1% per month³³. A systematic review compared the extended use of LMWH with a switch to coumadin in 1158 cancer patients and found that, compared with coumadin, long-term use of LMWH significantly reduced the risk of VTE recurrence (relative risk: 0.53; 95% CI: 0.36 to 0.76; $p = 0.007$), with no increase in the major bleeding risk³⁴.

4.3 Recurrent VTE

The rate of recurrent VTE despite ongoing anticoagulation remains high in cancer patients and is a commonly encountered clinical problem. A systematic review of 1292 patients with cancer showed that VTE recurrence rates in the LMWH and vitamin K antagonist groups using full (per label) doses were 6.5% and 17.9% ($p = 0.005$) respectively³⁵. When anticoagulation is inadequate or absent, VTE recurrence rates up to 50% after diagnosis of an initial acute VTE have been reported³⁶. A common strategy for the management of recurrent VTE is dose-escalation of the LMWH.

Beyond inadequate dosing, other causes of recurrent VTE include heparin-induced thrombocytopenia (HIT), dosing errors, noncompliance, and dramatic weight change. In a retrospective cohort study, 70 cancer outpatients referred for symptomatic recurrent VTE while receiving an anticoagulant were treated with either LMWH dose escalation (20%–25% for at least 4 weeks) or initiation of a therapeutic dose of LMWH (in those taking a vitamin K antagonist). The authors found a VTE recurrence rate of only 8.6% (95% CI: 4.0% to 17.5%) during the 3-month follow-up period³⁷. The opinion of the committee is that dose escalation can be an effective measure to regain control of thrombotic outcomes in cancer patients who recur while on treatment.

4.4 Incidental VTE

Incidental VTE is a PE or DVT discovered unintentionally through imaging or other investigations. A retrospective analysis that compared cancer patients experiencing incidental VTE with those experiencing symptomatic VTE showed no differences in VTE

recurrence, bleeding, and mortality³⁸. However, a case-control study showed that survival was significantly worse in cancer patients experiencing incidental VTE than in those not experiencing VTE (HR: 1.51; 95% CI: 1.01 to 2.27; $p = 0.048$)³⁹. A retrospective analysis of data from patients with pancreatic cancer found that DVT (HR: 25; 95% CI: 10 to 63; $p < 0.0001$), PE (HR: 8.9; 95% CI: 2.5 to 31.7; $p = 0.007$), and incidental visceral events (HR: 2.6; 95% CI: 1.6 to 4.2; $p = 0.0001$) were each independently associated with mortality⁴⁰. The risk for recurrent VTE in asymptomatic and symptomatic patients is equally high; therefore, although data are limited, clinical management is typically the same for incidental and symptomatic VTE. Patients with incidental VTE should receive anticoagulation therapy.

4.5 Patients with a CVC

Venous access is required for the management of some patients with cancer. However, the presence of a CVC can be associated with the development of upper extremity DVT⁴¹. A prospective study involving 74 patients with an active malignancy and acute symptomatic upper-extremity DVT used treatment with dalteparin 200 IU/kg daily for 5–7 days and warfarin (target INR: 2.0–3.0) and followed the patients for 3 months. No episodes of recurrent VTE were documented, and no lines were removed because of infusion failure or a recurrence or extension of DVT⁴².

Anticoagulation therapy for the duration of the CVC is recommended for cancer patients with upper-extremity DVT. The risk of recurrent VTE is highest in the first 3 months after resolution of the thrombus⁴³; therefore, in patients whose CVC has been removed, anticoagulation therapy for at least 3 months is recommended^{1–4}. Overall, there are no randomized data to guide management; however, based on the limited data available, the consensus was that, if a clot associated with a central line develops, and if the line is otherwise functional, it is reasonable to use anticoagulation to save the line. If line removal is deemed necessary (for example, the clot is causing symptoms such as pain or severe swelling), the patient should receive anticoagulation for at least 3 months.

4.6 Inferior Vena Cava Filter

The primary indication for insertion of an inferior vena cava (IVC) filter is the presence of acute DVT with a concurrent contraindication to anticoagulation^{44–47}. The addition of an IVC filter to antithrombotic therapy is generally not recommended. The PREPIC group randomized 400 patients with proximal DVT (with or without PE) treated with standard anticoagulation therapy for 3 months to either an IVC filter or no filter. After 8 years of follow-up, findings included a clinically small gain in the reduction of symptomatic PE (6.2% vs. 15.1%, $p = 0.008$), but an increase in the

incidence of DVT (35.7% vs. 27.5%, $p = 0.042$), and no difference in overall mortality⁴⁸. The same group of investigators followed up with a second RCT in 399 patients (PREPIC 2) that compared the addition of an IVC filter to anticoagulation with anticoagulation alone in patients with PE. All filters were removable (92.2% were successfully removed). The overall rate of PE was no different in the two groups⁴⁹. The addition of an IVC filter to pharmacologic anticoagulation therapy therefore has no supporting data. An IVC filter is not indicated for failure of anticoagulation, poor compliance with anticoagulation, or falls. Inferior vena cava filters are associated with high morbidity and can increase hypercoagulability. If placement is required, the filter should be removed as soon as the contraindication to anticoagulation therapy no longer exists; LMWH with an appropriate treatment duration can be started.

4.7 Patients with Renal Insufficiency

The risk of bleeding because of reduced renal excretion is higher in patients with renal impairment—that is, those with a creatinine clearance of 30 mL/min or less²⁸. Of the available LMWHs, tinzaparin has the highest average molecular weight (6500 Da), followed by dalteparin (6000 Da) and enoxaparin (4500 Da). Because of its high molecular weight, tinzaparin might be preferable in patients with renal insufficiency. A meta-analysis considered data from twenty treatment trials involving patients with a glomerular filtration rate less than 60 mL/min (half had a rate less than 30 mL/min). The included trials compared enoxaparin (typically 1 mg/kg every 12 hours) with UFH, fondaparinux, or tinzaparin, and treatment was given for a total of 1.5–10 days. The data revealed a significant increase in major bleeding with enoxaparin compared with the other anticoagulants (relative risk: 1.67; 95% CI: 1.12 to 2.50; $p = 0.01$); notably, however, the criteria used to measure major bleeding complications varied widely³¹. None of the available data are cancer-specific.

The data to suggest that anticoagulation with LMWH is safe in patients undergoing hemodialysis are insufficient; use of such therapy is therefore generally contraindicated in that population. A RCT comparing tinzaparin (175 IU/kg) and dalteparin (200 IU/kg) in 29 hemodialysis patients found that, pre-dialysis, mean levels of anti-factor Xa were 0.37 ± 0.23 IU/mL for tinzaparin and 0.62 ± 0.41 IU/mL for dalteparin ($p = 0.1$); however, 4 patients experienced serious adverse events (1 major bleed, 2 myocardial infarctions, and 1 upper-extremity DVT)⁵⁰. Treatment trials with tinzaparin and dalteparin in hemodialysis patients are ongoing; early reporting suggests clinically important bioaccumulation with both drugs⁵¹.

No RCTs have compared enoxaparin or dalteparin with other LMWHs, UFH, or vitamin K antagonists in elderly patients with cancer. The IRIS trial was a non-cancer-specific trial comparing tinzaparin with UFH

in 87 patients (mean age: 83 ± 5 years; range: 75–99 years) with a mean creatinine clearance of 40.8 mL/min. No significant accumulation was detected (mean accumulation ratio: 1.06; 90% CI: 1.01 to 1.11). No correlation between the accumulation ratio and age, weight, or creatinine clearance was observed. The trial was stopped prematurely because of a difference in mortality favouring the UFH group (11.5% vs. 6.3%, $p = 0.035$)^{29,30}. Data for dalteparin use in severe renal dysfunction are limited.

4.8 Patients with Thrombocytopenia

The risk of bleeding with respect to platelet count has not been well evaluated in any population of patients who require anticoagulation. Trials of anticoagulants typically exclude thrombocytopenic patients. Recommendations in this section are therefore based on consensus.

Bleeding risk is thought to be negligible in patients with an isolated thrombocytopenia at 50,000 cells/ μ L or more, but could increase when the platelet count is 20,000–49,000/ μ L. In patients with a platelet count below 20,000/ μ L, spontaneous and potentially fatal bleeding is typically felt to be more relevant. If anticoagulation is being considered in severely thrombocytopenic patients, assessment of the acuity of the thrombotic event is important (<4 weeks = acute; 4 weeks–3 months = subacute; >3 months = chronic).

For patients with acute VTE and a platelet count between 20,000/ μ L and 49,000/ μ L, the risk of recurrent VTE is still high; the panel therefore recommends platelet transfusion to maintain a platelet count above 50,000/ μ L to support full-dose anticoagulation. If platelet transfusions are not available or impossible to maintain (often more relevant in the outpatient setting), patients should be monitored very closely, and consideration of a LMWH dose reduction (that is, 50% dose) might be necessary.

After the acute phase has passed, the risk of recurrent VTE decreases significantly, and patients with severe thrombocytopenia might be more likely to bleed than to experience a recurrent clot. Therefore, in the non-acute VTE setting (that is, ≥ 4 weeks), the panel recommends dose-reduced anticoagulation (that is, a prophylactic dose) if platelets are 20,000–49,000/ μ L, with transition to a full therapeutic dose when platelets exceed 50,000/ μ L.

For patients with acute or non-acute VTE, the panel recommends stopping anticoagulation if the platelet count is less than 20,000/ μ L. A temporary IVC filter could be considered for those with acute DVT, but filter placement should be evaluated case by case. The panel suggests that, if the VTE is clinically significant (severe symptoms, recurrence or progression on reduced or held doses of LMWH, hemodynamic instability), hospital admission for platelet transfusion to maintain an arbitrary platelet count of at least 50,000/ μ L to support ongoing therapeutic

anticoagulation should be considered until the patient is stable. In unstable thrombocytopenic patients, expert opinion and consensus favour the use of UFH over other anticoagulants because of the possibility for dose titration and a relatively short half-life should emergency bleeding occur. If, at any platelet level, recurrent thrombosis or major bleeding occurs, any intensification, reduction, or cessation of therapy should be reassessed.

4.9 Patients with Liver Disease

In patients with comorbid liver disease who require anticoagulant therapy, LMWH generally appears to be safe. A non-blinded controlled trial⁵² randomized 70 ambulatory patients with advanced liver cirrhosis and patent portal veins to prophylactic subcutaneous enoxaparin (40 mg daily for 48 weeks) or to no treatment. The primary outcome was prevention of proximal vein thrombosis. An intention-to-treat analysis showed that, compared with no anticoagulant at all, enoxaparin was associated with less liver decompensation (38.2% vs. 83.0%, $p < 0.0001$), and no hemorrhagic events were reported. Nevertheless, some lower-level data suggested that patients with liver disease should be assessed case by case.

A retrospective multicentre chart review of 256 patients with chronic liver disease and an elevated INR (≥ 1.5) not secondary to anticoagulation showed differences in major and minor hemorrhage when comparing patients who did and did not receive VTE prophylaxis (17.5% vs. 7.4% respectively, $p = 0.02$). Factors independently associated with an increased risk of hemorrhage included pharmacologic VTE prophylaxis (adjusted odds ratio: 3.64; $p = 0.004$) and increased INR (adjusted odds ratio: 1.31; $p = 0.007$)⁵³. Although caution should be used, liver dysfunction is not an absolute contraindication to anticoagulation.

4.10 Monitoring Therapy

Routine anti-factor Xa monitoring in patients receiving therapeutic LMWH is not recommended. A RCT that compared fixed weight-based dosing with anti-factor Xa-adjusted dosing of dalteparin for DVT treatment showed no difference in any outcome. Thrombotic or bleeding outcomes and level of anti-factor Xa show no clear clinical correlations. In some select populations (extreme obesity, pregnancy, severe renal impairment), determination of anti-factor Xa levels can be helpful⁵⁴. In patients with significant renal insufficiency (creatinine clearance ≤ 30 mL/min), a check of trough levels of anti-factor Xa alongside clinical correlation to rule out drug accumulation is a reasonable approach. In patients for whom monitoring is considered, anti-factor Xa is the preferred test, and the target therapeutic range for twice-daily dosing in VTE is 0.5–1.1 IU/mL⁵⁴. Therapeutic levels for once-daily dosing are less clear, but a range of 1.0–2.0 IU/mL

could be considered⁵⁵. If the patient continues to experience recurrent thrombosis, referral to a thrombosis expert should be considered.

Use of heparin can be complicated by HIT, resulting in thrombocytopenia and thrombosis. The possibility of HIT should be investigated if the patient's platelet count falls by 50% or more, or if a thrombotic event occurs during days 5–14 after initiation of heparin (UFH or LMWH)⁵. Further, patients receiving heparin and considered to be at greater than 1% risk of HIT should be monitored for platelet count every 2–3 days from day 4 to day 14, or until heparin is stopped earlier⁵. The reported incidence rates for a new thrombosis and death from thrombosis in patients who simply discontinue heparin are 17%–56% and 11% respectively^{56–58}. Maintaining anticoagulation with a non-heparin-based alternative is therefore important. Prospective data have demonstrated efficacy with non-heparin agents such as lepirudin and argatroban, which, compared with simply stopping heparin or switching to a vitamin K antagonist, have been associated with a more than 70% decrease in the rate of new thromboses^{59–62}. The non-heparin anticoagulants that are currently approved for HIT in Canada include lepirudin, argatroban, and danaparoid. However, off-label bivalirudin and fondaparinux have also been used for this purpose. Only danaparoid has RCT evidence in HIT⁶³. In the absence of strong data on how to appropriately monitor for HIT in cancer patients on LMWH, the panel consensus favoured performing a baseline complete blood count before treatment initiation, with a repeat complete blood count within 1–2 weeks to evaluate the platelet count. If HIT is suspected, a HIT screen should be ordered, and referral to hematology should be considered.

4.11 Patient Education

There are no available data to inform the question of how best to educate patients about VTE. Recommendations about patient education are therefore consensus-based. Oncology professionals should educate patients about the signs and symptoms of VTE¹. In addition, consensus favoured the provision of personalized verbal and written instruction to patients about their condition and planned therapy, including side effects and drug interactions.

5. SUMMARY

This is the first national Canadian guideline on the prophylaxis and management 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. Acute VTE carries a high risk of morbidity and mortality, and most patients, including cancer patients, are safe

to initiate therapeutic anticoagulation. A longer duration of therapy is typically required for cancer patients because of the high risk of recurrent VTE. The favoured option for the treatment of VTE in patients with cancer is LMWH. Use of direct oral anticoagulants is currently not supported. Some subgroups of patients with cancer, including those with thrombocytopenia, renal insufficiency, and obesity could require modifications to their anticoagulant regimen. Monitoring of anti-factor Xa levels is not warranted in most patients. Patients with a history of VTE should be informed of their personal risk for recurrence, including signs and symptoms of recurrence.

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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.

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