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Prophylaxis and Treatment of Venus Thromboembolism in Patients Undergoing Treatment for Solid Tumours

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Cancer Care Alberta

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Background

Venous thromboembolism (VTE) is a vascular disorder characterized by deep vein thrombosis (DVT) and pulmonary embolism (PE).[1-4] DVT is characterized by a blood clot in the deep veins, typically in the legs but occasionally in the arms or pelvis; PE is characterized by a blood clot in an artery of the lung. Patients with cancer carry an increased risk of developing VTE due to tumour-mediated and treatment mediated hypercoagulability. Clinical risk factors for VTE in cancer include but are not limited to the primary site of cancer (e.g., highest risk sites include brain, pancreas, stomach, lung, bladder, testicular, gynecologic, kidney, lymphoma, myeloproliferative, and metastatic tumours), use of systemic therapy (i.e., chemotherapy, erythropoietic stimulating agents, exogenous estrogens, and antiangiogenic therapies), recent surgery, limited mobility, and hospitalization.[1, 5] In addition, the use of chemotherapy carries a relative risk 6.5 times greater than that of the general population.[6] A 2012 meta-analysis of 38 cohort studies comprising patients with cancer found that the overall risk of VTE in high-risk patients (i.e., those with metastatic disease or undergoing high-risk treatments) was more than 5-fold greater than that of average-risk patients.[4] Table 1 describes patient-related, cancer-related, and treatment-related factors that can adversely affect the risk of developing cancer-associated VTE.

Table 1. Factors associated with cancer-associated VTE.[6]

Category	Factors
Patient-related	• Increased age • Ethnicity (risk increased in African Americans) • Co-morbidities (infection, renal and pulmonary disease, arterial thromboembolism, VTE history, inherited prothrombotic mutations • Obesity Performance status
Cancer-related	• Primary site of 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 ≥ 60 mins • Erythropoiesis-stimulating agents (ESAs), transfusions • Indwelling venous access
Biochemical	• Leukocyte count >11,000/μL • Hemoglobin <100g/L

VTE rivals infection as the leading non-cancer cause of death in patients with cancer.[5, 7-9] The risk of dying after an acute thrombotic event is 4 to 8 times higher in patients with cancer than patients without cancer. The strongest predictor for recurrent VTE is a previous diagnosis of VTE.[10-13] VTE is also associated with long term complications including post-thrombotic syndrome and pulmonary hypertension.[14] The purpose of this guideline is to provide recommendations for physicians, nurses, and other front-line staff on the prophylaxis and treatment of VTE in patients with cancer, both in the inpatient and ambulatory settings.

Guideline Questions

1. What is the standard of care for ***ambulatory patients*** with solid tumours with established VTE? What is the standard pharmacologic therapy and dosing for the treatment of VTE?
2. Among ***ambulatory patients*** with solid tumours, who should receive prophylactic antithrombotic therapy for VTE? What is the standard pharmacologic therapy and dosing for the prophylaxis of VTE?
3. What is the standard of care for ***inpatients*** with solid tumours with established VTE? What is the standard pharmacologic therapy and dosing for the treatment of VTE?
4. Among ***inpatients*** with solid tumours, who should receive prophylactic antithrombotic therapy for VTE? What is the standard pharmacologic therapy and dosing for the prophylaxis of VTE?
5. How should patients be followed during the administration of antithrombotic therapy?
6. What are the most common complications of antithrombotic therapy use?

Search Strategy

MEDLINE and PubMed were searched for relevant articles published between 2002 and 2013. In addition, the American Society of Clinical Oncology (ASCO) and the National Guidelines Clearinghouse were searched, respectively, for meeting abstracts published between 2010 and 2013 and guidelines published between 2007 and 2013.

Search terms included “neoplasm” or “cancer” AND “venous thromboembolism” or “thrombosis” AND “thrombosis prophylaxis” or “VTE prophylaxis” and results were limited to randomized controlled trials (RCTs) and clinical trials (phase III-IV) published in English from 2002 to 2013 March 1, as well as meta-analyses published in English from 2008 to 2013 March 1. Studies that did not report outcomes related to the prophylaxis or treatment of VTE were excluded.

For the 2017 update a similar search strategy was conducted to cover the publication period from 2013 to July 2017. In addition, relevant product monographs were reviewed for updates. The full search strategy and evidence tables are available upon request.

Target Population

The recommendations in this guideline apply to adults over 18 years of age who are receiving treatment for **solid (i.e., non-hematologic) tumours**. Included are recommendations for inpatients and outpatients; however, the definition of an outpatient may vary by centre. Different

recommendations may apply to pediatric patients or patients receiving treatment for hematological malignancies, such as myeloma.

Recommendations

This guideline outlines the recommendations for VTE prophylaxis and treatment among adult patients with cancer. For the most current Alberta Health Services VTE-related clinical practice guidelines and policies for the general population please refer to:
https://extranet.ahsnet.ca/teams/policydocuments/1/Forms/AllItems.aspx

A patient resource for cancer patients is available at:
https://www.albertahealthservices.ca/assets/info/cca/if-cca-venous-thromboembolism.pdf

1. The use of antithrombotic agents is generally contraindicated in patients with active life-threatening bleeding, those who have had recent surgery, have pre-existing bleeding diathesis, low platelet counts (<30 x 10^9/L), or coagulopathy. Otherwise, antithrombotic therapy is relatively safe and most cancer patients are eligible for therapy at the discretion of the treating physician. A clinical algorithm for the use of antithrombotic therapy in patients with cancer is presented in Figure 1.

2. ***Ambulatory patient treatment***. Proximal lower extremity DVT and PE should be considered for antithrombotic therapy. In patients for whom antithrombotic therapy is not contraindicated, consider using one of the following:
    - Low molecular weight heparins (LMWH), dalteparin, enoxaparin or tinzaparin. Tinzaparin should be used for patients with non-dialysis dependent severe kidney failure (CrCl 20-30 mL per minute). No dose adjustment is needed. Administration is as follows:
        - Tinzaparin (175 units/kg/day subcutaneously [SC])
        - Dalteparin (200 units/kg/day SC for 1 month, then 150 units/kg/day SC)
            - The first month is dosed higher and then reduced as per the CLOT Trial.[15]
        - Enoxaparin (1 mg/kg SC twice daily or 1.5 mg/kg/day SC)
            - There is no consensus on dosage for cancer-associated thrombosis because there are no completed phase III trials in cancer patients

    - Direct oral anticoagulant agents (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban have not yet been proven to be efficacious or safe in oncology patients.

    - Although less favored, warfarin (5-10 mg/day orally, then adjust to international normalized ratio [INR] 2-3) may be used, especially in situations where LMWH is contraindicated, or if the patient refuses LMWH. Warfarin has been shown to be inferior to tinzaparin[16, 17] and dalteparin[15] in RCTs. There are no completed phase III trials comparing enoxaparin with warfarin. LMWH or unfractionated heparin (UFH) should be used to bridge warfarin until the INR is in the therapeutic range.

- There is no consensus on the duration of therapy. Trials using LMWH in cancer patients studied 3 to 6 months of treatment followed by standard of care at the discretion of the treating physician. Standard of care may include cessation of therapy, continuing LMWH, or switching to an oral agent. Patients with metastatic disease will continue to be at high risk for VTE and may be treated indefinitely at the discretion of the treating physician.[15, 16] For patients requiring longer treatment periods, two studies (TiCat and DALTECAN) have shown that LMWH treatment dosing in patients with cancer-associated thrombosis, up to a year is safe and efficacious.[18, 19]
- Renal function may change during treatment and should be monitored carefully.

3. ***Ambulatory patient prophylaxis***. High risk outpatients (i.e., patients with a risk factor score of three or more; see Table 3) **<u>may</u>** be considered for prophylactic antithrombotic therapy, at the discretion of the treating physician.

    - The recommended prophylactic antithrombotic therapy is LMWH, including any of the following:
        - Dalteparin (5,000 units/day SC)
        - Enoxaparin (40 mg/day SC or 30 mg SC twice daily)
        - Tinzaparin (4,500 units/day SC or 75 units/kg/day SC [for extremes of body weight])

    - Routine prophylactic anticoagulation is not recommended for ambulatory oncology patients by current guidelines.[20, 21]

    - The presence of a central venous catheter (CVC) in the absence of other risk factors is not an indication for the use of prophylactic antithrombotic therapy.

    - Current guidelines regarding VTE prophylaxis recommend extending postoperative prophylaxis up to 4 weeks for patients undergoing major abdominal or pelvic surgery with high-risk features.[21, 22] In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis considering the individual patient.

4. ***Inpatient treatment***. Proximal lower extremity DVT and PE should be considered for antithrombotic therapy.

    - LMWHs (i.e., dalteparin, enoxaparin or tinzaparin) are recommended. Tinzaparin should be used for patients with non-dialysis dependent severe kidney failure (CrCl 20-30 mL per minute). No dose adjustment is needed. Administration is as follows:
        - Tinzaparin (175 units/kg/day SC)

    - Dalteparin (200 units/kg/day SC for 1 month, then 150 units/kg/day SC)
        - The first month is dosed higher and then reduced as per the CLOT Trial.[15]
    - Enoxaparin (1 mg/kg SC twice daily or 1.5 mg/kg/day SC)
        - There is no consensus on dosage for cancer-associated thrombosis as there are no completed phase III trials.
        - For some physicians 1 mg twice daily or 1.5 mg/kg/day is acceptable.

- Direct oral anticoagulant agents (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban have not yet been proven to be efficacious or safe in oncology patients.

- Although less favored, warfarin (5-10 mg/day orally, then adjust to INR 2-3) may be used, especially in situations where LMWH is contraindicated or if the patient refuses LMWH. Warfarin has been shown to be inferior to tinzaparin[16, 17] and dalteparin[15] in RCTs. There are no completed phase III trials comparing enoxaparin with warfarin. LMWH or UFH should be used to bridge warfarin until the INR is in the therapeutic range.

- Unfractionated heparin (UFH) may be used at the discretion of the treating physician under select circumstances only (e.g., when rapid clearance of anticoagulants is desired). UFH is typically given as 80 units/kg intravenously, then 18 units/kg/hour or as per electronic medical record algorithms or validated online dosing calculators based on partial thromboplastin time.

- There is no consensus on the duration of therapy. Trials using LMWH in cancer patients studied 3 to 6 months of treatment followed by standard of care at the discretion of the treating physician. Standard of care may include cessation of therapy, continuing LMWH, or switching to an oral agent. Patients with metastatic disease will continue to be at high risk for VTE and may be treated indefinitely at the discretion of the treating physician.[15, 16] For patients requiring longer treatment periods, two studies (TiCat and DALTECAN) have shown that LMWH treatment dosing in patients with cancer-associated thrombosis, up to a year is safe and efficacious.[18, 19]

- Patients scheduled for surgery, according to perioperative management of antithrombotic therapy guidelines published in the Chest Journal, should stop LMWH 24 hours prior to surgery or UFH 4-6 hours prior to surgery.[23] Therapeutic doses of LMWH and UFH should not be re-started until the high-risk period for bleeding is over at physician discretion (typically at least 3 days post-surgery). Prophylactic LMWH or UFH for DVT prophylaxis can be initiated earlier if hemodynamically stable (often on post-operative day 1).
- Renal function may change during treatment and should be monitored carefully.

5. ***Inpatient prophylaxis****.* Patients admitted as inpatients should receive antithrombotic therapy for DVT prophylaxis unless contraindicated. Non-pharmacologic prophylaxis (e.g., compression stockings) and early mobilization can be considered for patients unable to receive pharmacologic agents (typically those who are actively bleeding).

    - The recommended prophylactic antithrombotic therapy is LMWH, including any of the following:
        - Dalteparin (5,000 units/day SC)
        - Enoxaparin (40 mg/day SC or 30 mg SC twice daily)
        - Tinzaparin (4,500 units/day SC or 75 units/kg/day SC [for extremes of body weight])
    - The presence of a CVC in the absence of other risk factors is not an indication for the use of prophylactic antithrombotic therapy.

6. ***Special clinical scenarios.*** Appendix I describes various clinical scenarios that can influence the use of antithrombotic agents as treatment or prophylaxis.

7. ***Follow-up.*** Follow-up visits should ensure that self-injections are administered properly and assess for bleeding complications. Follow-up should occur initially at either one week or one month after starting antithrombotic therapy, and then at six months. A baseline complete blood count (CBC) is required to ensure anticoagulation is safe; severe thrombocytopenia may require dose adjustment or non-antithrombotic alternatives. For patients receiving heparin in whom clinicians consider the risk of heparin induced thrombocytopenia (HIT) to be >1%, CBC should be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) to assess for HIT, a rare but life threatening complication of heparin-based therapy.

8. ***Complications.*** Bleeding is the most common complication of anticoagulation therapy. Major bleeding while on anticoagulation requires immediate cessation of all antithrombotic therapy and presentation to an emergency department where an appropriate treatment algorithm can be initiated. Minor bleeding can be assessed in clinic and may require anticoagulant cessation at the discretion of the physician.

9. ***Survival.*** Anticoagulation is not recommended for use in extending survival in patients with cancer in the absence of other indications for anticoagulation.

10. ***Patient Education.*** Patients and their caregivers should be informed about VTE prophylaxis and treatment by health care professionals with oncology experience. Patients should also be trained in self-injection with the assistance of a clinic nurse. Items that should be reviewed include:
    - VTE risk and options to lower the risk;
    - symptoms of a blood clot, particularly PE, and what to do if one is suspected;
    - blood clot prevention;

- purpose of anticoagulation medication;
- administration route;
- chance of benefit from treatment versus possible side effects;
- restrictions when on anticoagulation medication (e.g., alcohol in moderation); and
- post-thrombotic syndrome

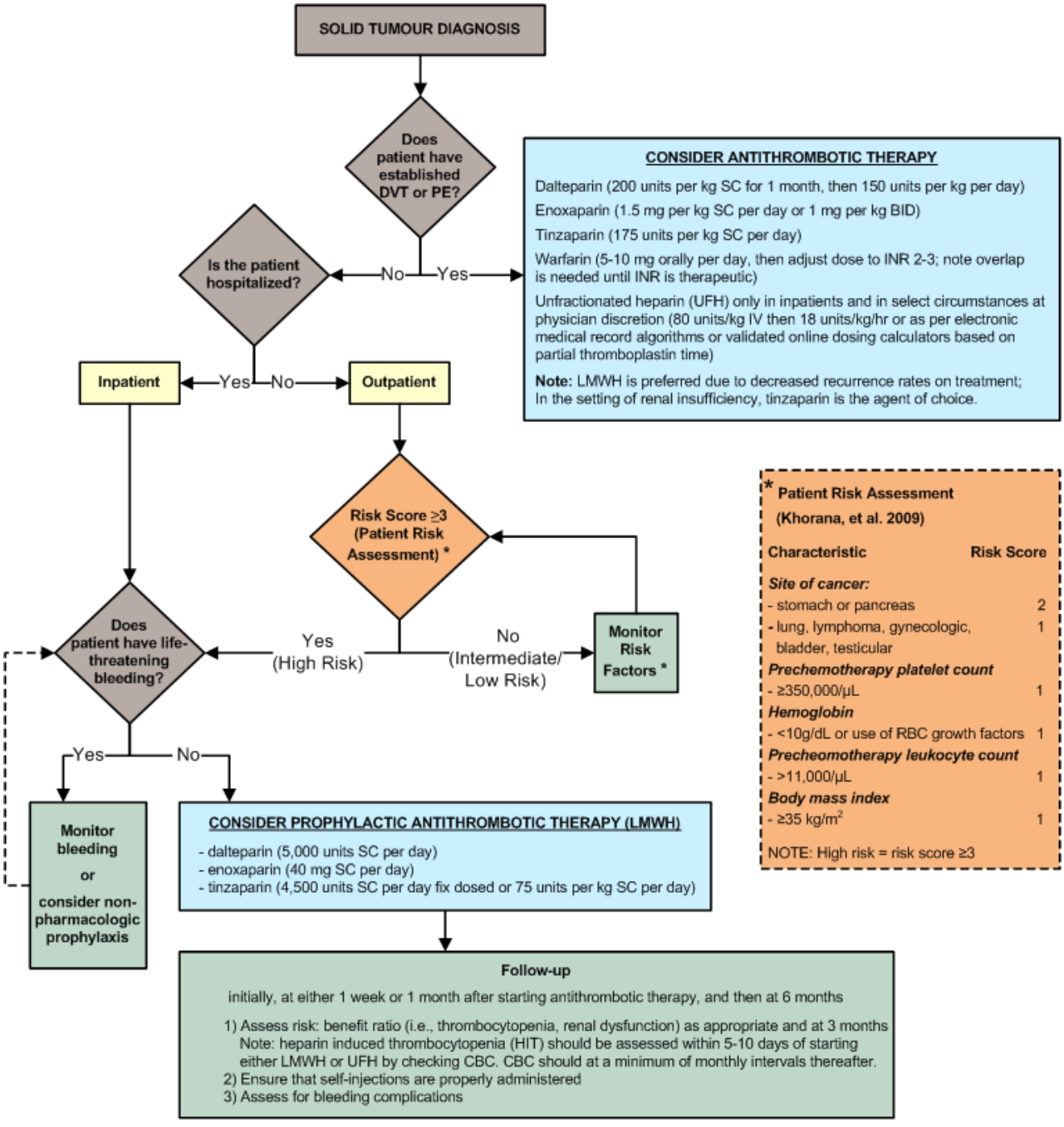

Figure 1. Algorithm for VTE prophylaxis and treatment in patients with solid tumours.

Discussion

Treatment for Established VTE Using Anticoagulation Therapy

VTE typically presents as DVT or PE. The signs and symptoms of DVT include pain, edema/swelling in the limbs or upper body, persistent cramping, and erythema, whereas the signs and symptoms of PE include, but are not limited to chest pain, shortness of breath, hypoxia, tachycardia, and tachypnea.[24] None of the signs or symptoms of DVT and PE are sensitive or specific for VTE and a high index of suspicion should be present in patients with these symptoms who also have substantial risk for VTE, such as cancer patients. In addition to a clinical evaluation, imaging is required to diagnose DVT (i.e., venous ultrasound) and PE (i.e., CT angiography [CTA] with contrast, MRI angiography with contrast, or ventilation/perfusion scan if CTA is contraindicated).[25] Initial therapy for established VTE should be a LMWH.[21, 24-26]

For maintained anticoagulation, LMWH has been shown to be more effective than warfarin therapy in patients on active cancer treatment. The CLOT trial (Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer), which included cancer patients with acute, symptomatic proximal DVT, PE, or both (n=672), compared LMWH (i.e., dalteparin) with daily warfarin as maintenance therapy.[15] All patients were initially treated for 6 months with either dalteparin (200 IU per kg per day subcutaneously for 1 month and 150 IU per kg per day for 5 months) or warfarin (INR 2-3) for 6 months. Recurrent VTE occurred in 8% (27/336) of the dalteparin group versus 16% (53/336) of the warfarin group (HR 0.48; p=.002). Major bleeding and any bleeding did not differ between groups (6% vs. 4% and 14% vs. 19%, respectively). The LITE trial compared tinzaparin with warfarin for 3 months in patients with cancer and acute symptomatic proximal-DVT (n=200).[16] Recurrent VTE occurred in 7% (7/100) of the tinzaparin group versus 16% (16/100) of the VKA group (RR 0.44; p=.044). Bleeding did not differ between groups (27% vs. 24%). One new RCT, CATCH, compared tinzaparin to warfarin for 6 months in patients with active cancer and proximal DVT or PE (n=900).[17] Recurrent VTE occurred in 7.2% (31/449) of patients treated with tinzaparin versus 10.5% (45/451) of patients treated with warfarin (p=.07), and there were no differences in major bleeding (p=.07). 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 12.3-32.4) for warfarin versus 10.5% (95% CI 4.3-20.3) for enoxaparin (p=.09).[27] However, the study was stopped early because of poor accrual.

VTE Prevention Using Anticoagulation Therapy

Because patients with a prior episode of VTE are at risk of recurrence, coupled with the increased risk of mortality from VTE when cancer is present, prophylaxis is an important consideration in the care of patients with cancer, especially those with active risk factors (i.e., erythropoietic stimulating agent use, exogenous estrogen use, antiangiogenic therapy use, and recent surgery).[5, 10-13] A model

developed by Khorana, et al. may be useful in assessing VTE risk, based on specific patient factors (Table 3).[5, 9]

Table 3. Predictive model for chemotherapy-associated VTE* [5]

Patient Characteristic	Risk Score	Risk of VTE
Site of cancer		
Very high risk (stomach, pancreas, brain)	2	Score ≥3 = 7%
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1	
Prechemotherapy platelet count ≥350,000/μL	1	Score 1-2 = 2%
Hemoglobin <100g/L or use RBC growth factors	1	
Prechemotherapy leukocyte count >11,000/μL	1	Score 0 = 0.5%
Body mass index ≥35 kg/m^2	1	

**high risk is defined as a risk score of three or more*

Several meta-analyses on the role of VTE prophylaxis have been performed and include patients with central venous catheters,[28] patients receiving chemotherapy,[29] and patients with cancer undergoing surgery.[30] In a meta-analysis evaluating the relative efficacy and safety of anticoagulation for thromboprophylaxis in people with cancer with a CVC, the authors reported that compared with no anticoagulation, there was a statistically significant reduction of symptomatic DVT with heparin (RR 0.48; 95% CI 0.27-0.86) and asymptomatic DVT with VKA (RR 0.43; 95% CI 0.30-0.62). Heparin was associated with a higher risk of thrombocytopenia (RR 3.73; 95% CI 2.26-6.16) and asymptomatic DVT when compared with VKA (RR 1.74; 95% CI 1.20-2.52). However, the findings did not rule out other clinically important benefits and harms. A Cochrane systematic review of 26 RCTs that included 12,352 ambulatory cancer patients receiving chemotherapy showed that compared with no thromboprophylaxis, LMWH significantly reduced the incidence of symptomatic VTE (RR 0.54, 95% CI 0.38-0.75) with a non-statistically significant 44% higher risk of major bleeding events (RR 1.44, 95% CI 0.98-2.11).[29] Another meta-analysis evaluating the relative efficacy and safety of LMWH and UFH for perioperative thromboprophlaxis in patients with cancer did not conclusively rule out either a beneficial or harmful effect of LMWH compared with UFH for: mortality (RR 0.89; 95% CI 0.74 to 1.08), PE (RR 0.73; 95% CI 0.34-1.54), symptomatic DVT (RR 0.50; 95% CI 0.20-1.28), asymptomatic DVT (RR 0.81; 95% CI 0.66-1.01), major bleeding (RR 0.85; 95% CI 0.52-1.37), and minor bleeding (RR 0.92; 95% CI 0.47-1.79).[30]

Table 4 provides a brief summary of phase III RCTs on the use of anticoagulation agents for VTE prophylaxis.

Table 4. Phase III RCTs on the use of anticoagulation agents for VTE prophylaxis.

Author Year (Trial)	Phase	Agent	Control	Patient Characteristics	Events (VTE)		
					agent	control	p-value
Pelzer 2015 (CONKO-004)[31]	III	enoxaparin	control	pancreatic tumours (n=312)	6.4%	15.1%	p=.001
Agnelli 2012 (SAVEONCO)[32]	III	semuloparin	placebo	solid tumours, pre-chemo (n=3216)	1.2%	3.4%	p<.001
Maraveyas 2012 (FRAGEM)[33]	III	dalteparin	control	pancreatic tumours (n=123)	12.0%	28.0%	p=.04
Haas 2012 (TOPIC-2)[34]	III	certoparin	placebo	NSCLC, chemo (n=353)	4.5%	8.3%	
Larocca 2012[35]	III	enoxaparin	aspirin	MM, lenalidomide (n=342)	1.2%	2.3%	p=.45
Kakkar 2011 (LIFENOX)[36]	III	enoxaparin	placebo	acutely ill (n=8307; 5.9% cancer)	0.2%	0.1%	
Palumbo 2011[37]	III	enoxaparin	warfarin	MM, thalidomide (n=667)	3.2%	8.2%	p=.02
Haas 2011 (CERTIFY)[38]	III	certoparin	UFH	solid tumours (n=274)	4.5%	6.0%	
Kessler 2011[39]	III	LMWH	control	MM, chemo (n=258)	3.4%	12.9%	p=.007
Agnelli 2009 (PROTECHT)[40]	III	nadroparin	placebo	solid tumours, chemo (n=1168)	2.0%	3.9%	p=.02
Kakkar 2010 (CANBESURE)[41]	III	bemiparin	placebo	cancer surgery (n=625)	0.8%	4.6%	p=.01
Perry 2010 (PRODIGE)[42]	III	dalteparin	placebo	glioma, no chemo (n=186)	9.1%	14.9%	p=.29
Hull 2010 (EXCLAIM)[43]	III	enoxaparin	placebo	acutely ill (n=5963; 1.6% cancer)	2.5%	4.0%	
Young 2009[44]	III	warfarin	control	cancer, chemo, CVC (n=1590)	6.0%	6.0%	p=.98
Karthaus 2006[45]	III	dalteparin	placebo	cancer, chemo (n=439)	3.7%	3.4%	p=.88
Simonneau 2006[46]	III	nadroparin	enoxaparin	cancer surgery (n=1288)	15.9%	12.6%	
Verso 2005[47]	III	enoxaparin	placebo	cancer, CVC (n=321)	14.1%	18.0%	
Couban 2005[48]	III	warfarin	placebo	cancer, CVC (n=255)	1.6%	4.0%	
Abdelkefi 2004[49]	III	LD-UFH	placebo	hematological cancer (n=128)	1.5%	12.6%	p=.03
Kakkar 2004 (FAMOUS)[50]	III	dalteparin	placebo	solid tumours (n=385)	2.4%	3.3%	
Minnema 2004[51]	III	nadroparin	control	MM (n=412)	5.0%	9.0%	p=.15

VTE = venous thromboembolism; NSCLC = non-small cell lung cancer; MM = multiple myeloma; LD = low dose; UFH = unfractionated heparin; LMWH = low molecular weight heparin; CVC = central venous catheter

Direct Oral Anticoagulants

DOACs are attractive because of their predictable response, oral administration, and fixed-dose regimens. However, only a small proportion of patients with cancer have been included in RCTs assessing their efficacy and safety. Several meta-analyses have extracted data from these trials with the aim of assessing the efficacy and safety of DOACs in patients with VTE and cancer.[52-55] A meta-analyses that included six studies found that VTE recurred in 3.9% and 6.0% patients with cancer treated with DOACs and conventional treatment (VKAs), respectively (OR 0.63; 95% CI, 0.37-1.10). Major bleeding occurred in 3.2% and 4.2% of patients receiving DOACs and conventional treatment, respectively (OR 0.77; 95% CI, 0.41-1.44).[52] While DOACs seem to be as effective and safe as conventional treatment for the prevention of VTE in patients with cancer, more clinical trials are needed to confirm these results, directly compare new agents, and compare DOACs to LMWHs. Results from the Hokusai VTE-cancer study, a randomized, open-label, clinical trial evaluating

whether edoxaban, is non-inferior to LMWH (dalteparin) for treatment of VTE in patients with cancer are awaited.[55] For patients who refuse or have compelling reasons to avoid LMWH, National Comprehensive Cancer Network (NCCN) guidelines state that for acute management of VTE, apixaban and rivaroxaban are acceptable alternatives, and for chronic management, apixaban, dabigatran, edoxaban, and rivaroxaban are all acceptable second-line agents.[25]

Anticoagulation Therapy and Survival

It is not recommended that anticoagulation be used to extend survival in patients with cancer in the absence of other indications for anticoagulation.[21, 56] A meta-analysis of RCTs (n=9) evaluating the use of LMWH versus placebo or no anticoagulant in cancer patients without venous thrombosis found no discernible effect on mortality with the use of LMWH (OR for 1-year mortality 0.87, 95% CI 0.70-1.08).[57] A Cochrane review evaluated the efficacy and safety of parenteral anticoagulants in ambulatory cancer patients with no standard therapeutic or prophylactic indication for anticoagulation.[58] In all included RCTs (n=15) the intervention consisted of heparin (either UFH or LMWH). The results showed that heparin may have a small effect on mortality at 12 months and 24 months (RR 0.97; 95% CI 0.92-1.01 and RR 0.95; 95% CI 0.90-1.00, respectively). Another Cochrane Review evaluated the efficacy and safety of oral anticoagulants in patients with cancer with no therapeutic or prophylactic indication for anticoagulation.[59] The oral anticoagulant was warfarin in six of the seven RCTs included. The comparator was either placebo or no intervention. The use of warfarin had no effect on mortality at six months (RR 0.98; 95% CI 0.82-1.22), one year (RR 0.97; 95% CI 0.89-1.04), two years (RR 0.98; 95% CI 0.81-1.18), or five years (RR 0.92; 95% CI 0.83-1.01).

Contraindications and Side Effects of Anticoagulation Therapy

The use of antithrombotic agents is generally contraindicated in patients with active life-threatening bleeding, those who have had recent surgery, have pre-existing bleeding diathesis, low platelet counts, or coagulopathy. Acute VTE carries a significant risk of early recurrence/extension/ embolization in the absence of anticoagulation even in thrombocytopenic patients. Thus, anticoagulant options for patients with a platelet count <50,000μL should be reviewed with a specialist and be closely monitoring on or off anticoagulation. Decisions about treatment and dosage should be made on a case-by-case basis with the utmost caution. Otherwise, anticoagulation therapy is relatively safe and most patients should be eligible. The most common side effect of anticoagulant therapy is bleeding. According to a meta-analysis, the rate of major bleeding with LMWH is only slightly greater than that of placebo (2.5% vs. 1.7%).[60] As compared to UFH, the risk of major bleeding with LMWH is not significantly different (RR 0.85; 95% CI 0.52-1.37).[30] The risk of bleeding from antithrombotic therapy must be weighed against the possible therapeutic benefits; however, overall anticoagulant therapy appears to be safe in patients without active bleeding. Major bleeding associated with enoxaparin, dalteparin, and tinzaparin is low (<1%).

The risk of bleeding because of reduced renal excretion is higher in patients with renal impairment (i.e., those with a creatinine clearance [CrCl] ≤30 mL/min).[61] 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. In patients being treated with tinzaparin (175 IU/kg) for DVT, a population pharmacokinetic analysis showed a reduction in tinzaparin clearance in moderate (30-50 mL/min) and severe (<30 mL/min) renal impairment.[62] Patients with severe renal impairment exhibited a reduction in tinzaparin clearance relative to patients with normal renal function (>80 mL/min). However, available evidence demonstrates no accumulation in patients with CrCl levels down to 20 mL/minute. There is limited data available in patients with an estimated CrCl level below 20 mL/minute. Data for dalteparin use in severe renal dysfunction are limited. 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 (RR 1.67; 95% CI: 1.12-2.50; p=.01); notably, however, the criteria used to measure major bleeding complications varied widely.[63] Data for dalteparin use in patients with advanced or severe renal impairment (CrCl <30 mL/min) are limited. In a re-analysis of data from the CLOT trial, patients with cancer who had acute VTE and impaired renal function at baseline (CrCl <60 ml/min) demonstrated an 86.5% relative risk reduction of developing recurrent VTE when treated with dalteparin versus VKA.[64] Patients with normal renal function (CrCl >60 ml/min) only demonstrated a 43.6% relative risk reduction. While bleeding event rates for both treatments were reported to be similar (p=.47), in the dalteparin treatment group, rates of any bleeding and major bleeding were almost twice as high in patients with renal impairment as in patients with normal renal function, respectively (20.3 and 11.8% for any bleeding; 9.5 and 4.1% for major bleeding). These findings suggest that dalteparin might accumulate in patients with renal impairment. Of note, anti-Xa levels were not reported.

Challenges with Using Low Molecular Weight Heparin

Described below are examples of scenarios that may prove challenging for physicians wanting to provide VTE prophylaxis or treatment using LMWH.

Liver cirrhosis. A RCT in patients with advanced cirrhosis showed that compared to observation, enoxaparin was associated with less liver decompensation (38.2% vs. 83.0%; p<.0001) with no hemorrhagic events reported.[65] Based on this evidence, LMWH can be used in patients with liver disease, at the discretion of the treating physician. As well, on the basis of pharmacokinetics (i.e., antifactor Xa activity), prophylactic LMWH appears to be safe in this population.[66]

Inferior vena cava (IVC) filter. Indications for the use of an IVC filter include, but are not limited to, contraindication to anticoagulation, as well as the presence of VTE while bleeding or at risk for bleeding.[67-69] Failure of anticoagulation, poor compliance with anticoagulation, and falls are not indications for an IVC filter. Changing or intensifying anticoagulation, appropriate patient counseling, increased patient monitoring and interventions to decrease bleeding risk can be explored in such

situations. IVC filters are associated with high morbidity and can increase hypercoagulability. Therefore, if placement is required they should be removed as soon as possible (e.g., once the bleeding risk is low or when the contraindication to anticoagulation therapy no longer exists and LMWH can be started). There are no data to support the addition of an IVC filter to pharmacologic anticoagulation therapy.[70] Conversely, patients with an IVC filter who can receive pharmacologic anticoagulation therapy should continue treatment as long as they are deemed at high risk of recurrent VTE regardless of presence or absence of the filter. Contraindications to anticoagulation include a high risk for bleeding, current bleeding, and severe thrombocytopenia.[68, 69]

Patients scheduled for surgery. Because of the bleeding risk associated with surgery, caution must be used in patients already taking anticoagulation therapy. According to perioperative management of antithrombotic therapy guidelines published in *Chest*, patients scheduled for surgery should stop LMWH approximately 24 hours prior to surgery or UFH 4 to 6 hours prior to surgery.[23] In patients undergoing high-bleeding risk surgery, therapeutic-dose LMWH should not be resumed until 48 to 72 hours after surgery. In patients who require a minor dental procedure, it is recommended to continue VKAs with coadministration of an oral prohemostatic agent or stop VKAs 2 to 3 days before the procedure. In patients who require minor dermatologic procedures and are receiving VKA therapy, VKAs can be continued around the time of the procedure with optimized local hemostasis. In patients who require cataract surgery and are receiving VKA therapy, VKAs can also be continued around the time of the surgery.

ASCO guidelines recommend that patients undergoing major surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days. Extending prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features.[21] The American College of Chest Physicians also recommend that high-risk patients undergoing abdominal or pelvic cancer surgery receive extended prophylaxis for up to four weeks.[22] These recommendations are supported by a Cochrane review that analyzed data from four clinical trials among patients undergoing major abdominal or pelvic surgery and found that the incidence of overall VTE (DVT and PE) and symptomatic VTE was lower in the extended LMWH group (respectively: 14.3% vs. 6.1%; p<.0005 and 1.7% vs. 0.2%; p=.02).[71] There is limited evidence on the effect of LMWH on bleeding risk following a biopsy. A retrospective study among children (n=190) undergoing ultrasound-guided liver biopsies showed that for three major and 28 minor bleeding incidents, the LMWH was a risk factor.[72] Patients scheduled to receive a biopsy could be treated as patients scheduled for low-risk bleeding surgeries at the discretion of the treating physician.

Low platelet count (thrombocytopenia). Recommendations published in international clinical practice guidelines state that in cancer patients with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 x 10^9/L and there is no evidence of bleeding.[73] For cancer patients with a platelet count <50 x 10^9/L the guidelines recommend that treatment decisions be made on an individual basis with an abundance of caution. ASCO guidelines do not recommend anticoagulant prophylaxis or therapy in patients with a platelet count <50 x 10^9/L.[21] Only the monograph for dalteparin provides specific dose reduction instructions: “In the case

of chemotherapy-induced thrombocytopenia with platelet counts <50 x 10^9/L, dalteparin should be interrupted until the platelet count recovers above 50 x 10^9/L. For platelet counts between 50 x 10^9/L and 100 x 10^9/L, dalteparin should be reduced by 17% to 33% of the initial dose (allowing for dosage adjustments using the prefilled syringes), depending on the patient's weight. Once the platelet count recovers to ≥100 x 10^9/L, dalteparin should be-instituted at full dose."[74]

Heparin-Induced Thrombocytopenia (HIT). HIT is thrombocytopenia that occurs as the result of heparin use. The American College of Chest Physicians recommend that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) for patients receiving heparin in whom clinicians consider the risk of HIT to be >1%.[75] In patients with HIT with thrombosis the use of nonheparin anticoagulants (i.e., lepirudin, argatroban, and danaparoid) are recommended. In patients with strongly suspected or confirmed HIT, VKA is not recommended until after platelets count have substantially recovered (usually, to at least 150 x 10^9/L). VKA should be started in low doses (max 5 mg of warfarin or 6 mg phenprocoumon) over higher doses. A history of confirmed or suspected HIT is a contraindication for use of LMWH and UFH.

Obesity. Obesity is a risk factor for VTE. Enoxaparin and dalteparin have been studied in obese patients (body mass index ≥ 30). These studies suggest that in obese patients LMWH should be dosed to the patient's actual body weight, not ideal body weight.[76, 77] A pharmacodynamic study looking at tinzaparin weight-adjusted dosing in obese patients (101-165 kg; 26-61 kg/m^2) found that anti-Xa levels were not affected by body weight or body mass index. As such, tinzaparin can be safely dosed to the patient's actual body weight.[78]

Incidental VTE. Occasionally, VTE (e.g., PE, DVT, splanchnic or visceral vein thrombi) is found incidentally on routine scanning. Rates of VTE recurrence and mortality seem to be similar in patients with cancer and incidental VTE as compared with those with symptomatic VTE.[79, 80] Incidental VTE may be treated the same way as symptomatic VTE.

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Appendix A: Recommended Use of Antithrombotic Agents in Special Clinical Scenarios

Platelet Count <50,000/µL (Thrombocytopenia)

- Dose reductions are not absolutely necessary for platelet counts between 50,000-100,000/µL, but may be considered at the discretion of the treating physician.[74, 81, 82]
- Use of LMWH should be made on a case-by-case basis with utmost caution if platelets <50,000/µL.

Scheduled for Surgery and Currently Taking Anticoagulant Therapy[21, 23]

- LMWH should be stopped 24 hours prior to surgery.
- UFH should be stopped 4-6 hours prior to surgery.
- LMWH should not be re-started in patients undergoing high-bleeding-risk surgery for 2 to 3 days post-surgery.
- Bridging anticoagulation is recommended in patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, during interruption of vitamin K antagonist (VKA) therapy.
- Extension of LMWH prophylactic therapy for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis considering the individual patient.

Liver Disease

- LMWH can be used at the discretion of the treating physician.

CNS Malignancy

- Anticoagulation is recommended for established VTE; however, careful monitoring is necessary to limit the risk of hemorrhage.[6]

Inferior Vena Cava (IVC) Filter in Place

- Indications for an IVC filter insertion include contraindication to anticoagulation and presence of VTE while bleeding or at risk for bleeding.
- IVC filters are associated with high morbidity and can increase hypercoagulability; therefore, they should be removed as soon as possible (e.g., once the bleeding risk is low or when the contraindication to anticoagulation therapy no longer exists and LMWH can be started).
- There are no data to support the addition of an IVC filter to pharmacologic anticoagulation therapy. However, patients with an IVC filter who can receive pharmacologic anticoagulation therapy should continue pharmacologic treatment as long as they are deemed at high risk of recurrent VTE regardless of presence or absence of the filter.[83]

Impaired Renal Function

- CrCL >30 mL/min: use dalteparin,[74] tinzaparin,[62, 84] or enoxaparin [85]
- CrCL 20-30 mL/min: use tinzaparin[62, 84]
- CrCL <20 mL/min: do not use LMWH; use unfractionated heparin plus warfarin

Heparin-Induced Thrombocytopenia (HIT)[75, 86]

- HIT occurs as the result of heparin use (e.g., UFH or LMWH).
- Consultation with a hematologist may be appropriate.
- Patients receiving heparin in whom clinicians consider the risk of HIT to be >1% should have platelet count monitoring performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first).
- Patients with HIT with thrombosis should use nonheparin anticoagulants (i.e., lepirudin, argatroban, and danaparoid), over the further us of heparin or LMWH or initiation/continuation of a VKA.
- Strongly suspected or confirmed HIT should not be treated with VKA until platelets have substantially recovered (≥150 x 10^9/L); VKA should be restarted in low doses (max 5 mg of warfarin or 6 mg phenprocoumon).
- The risk of HIT is lower with LMWH vs. UFH (RR 0.23, 95% CI 0.07-0.73); the risk of HIT complicated by VTE is also lower with LMWH vs. UFH (RR 0.22, 95% CI 0.06-0.84).

Obesity[21]

- Dose LMWH to actual body weight not ideal body weight.

Central Venous Catheter (CVC)-Related VTE[87]

- 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
- Anticoagulation therapy for at least 3 months is recommended for cancer patients with upper-extremity DVT in whom the CVC has been removed

Incidental VTE[21]

- Anticoagulation with LMWH is recommended.

Palliative Care

- Patients undergoing active treatment with palliative chemo- and radiotherapy who are receiving anticoagulation therapy should continue to do so; however, once palliative therapy is withdrawn, risks/discomfort/inconveniences of anticoagulation should be re-weighed against the benefits of preventing recurrent VTE (which may be negligible in the end stages of life). Anticoagulation may be stopped at physician discretion.

Elderly

- Tinzaparin may have a better safety profile in elderly patients with renal dysfunction.[84, 88]
- Tinzaparin should be used in the elderly in standard doses.[62]

Development and Revision History

This guideline was reviewed and endorsed by members of the Alberta Provincial Tumour Teams, including medical oncologists, radiation oncologists, surgeons, hematologists, nurses, pathologists, physiotherapists, and pharmacists.

Evidence was selected and reviewed by a working group comprised of a medical oncologist and a methodologist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Methodology Handbook.

Maintenance

A formal review of the guideline is scheduled to be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; ASCO, American Society of Clinical Oncology; BID, twice per day; CBC, complete blood count; CVC, central venous catheter; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low molecular weight heparin; PE, pulmonary embolism; RCT, randomized controlled trial; UFH, unfractionated heparin; VKA, Vitamin K antagonist; VTE, venous thromboembolism;

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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