PROPHYLAXIS AND TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS UNDERGOING TREATMENT FOR SOLID TUMOURS

Effective Date: February 2014

The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Program 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.
BACKGROUND

Venous thromboembolism (VTE) is a vascular disorder characterized by deep vein thrombosis (DVT) and pulmonary embolism (PE). 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. In addition, the use of chemotherapy carries a relative risk 6.5 times greater than that of the general population. 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. 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

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
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<tbody>
<tr>
<td>Patient-related</td>
<td>Increased age</td>
</tr>
<tr>
<td></td>
<td>Ethnicity (risk increased in African Americans)</td>
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<td></td>
<td>Co-morbidities (infection, renal and pulmonary disease, arterial thromboembolism, VTE history, inherited prothrombotic mutations)</td>
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<td>Obesity Performance status</td>
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<td>Cancer-related</td>
<td>Primary site of cancer</td>
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<td></td>
<td>Stage (risk increases with higher stage)</td>
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<td></td>
<td>Comorbid conditions</td>
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<td></td>
<td>Histology</td>
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<tr>
<td></td>
<td>Time since diagnosis (risk increases during first 3-6 months)</td>
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<tr>
<td>Treatment-related</td>
<td>Chemotherapy, antiangiogenesis agents, hormonal therapy</td>
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<tr>
<td></td>
<td>Radiation therapy</td>
</tr>
<tr>
<td></td>
<td>Surgery ≥ 60 mins</td>
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<tr>
<td></td>
<td>Erythropoiesis-stimulating agents (ESAs), transfusions</td>
</tr>
<tr>
<td></td>
<td>Indwelling venous access</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Leukocyte count &gt;11,000/µL</td>
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<tr>
<td></td>
<td>Hemoglobin &lt;100g/L</td>
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</tbody>
</table>

Venous thromboembolism rivals infection as the leading non-cancer cause of death in patients with cancer. 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. VTE is also associated with long term complications including post-thrombotic syndrome and pulmonary hypertension. 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

- 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?

- Among ambulatory patients with solid tumours, who should receive prophylactic antithrombotic therapy for venous thromboembolism (VTE)? What is the standard pharmacologic therapy and dosing for the prophylaxis of VTE?

- 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?

- Among inpatients with solid tumours, who should receive prophylactic antithrombotic therapy for venous thromboembolism (VTE)? What is the standard pharmacologic therapy and dosing for the prophylaxis of VTE?

- How should patients be followed during the administration of antithrombotic therapy?

- What are the most common complications of antithrombotic therapy use?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Tumour Program. Members of the Alberta Provincial Tumour Program include 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 research methodologist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU handbook. 15

SEARCH STRATEGY

The National Library of Medicine’s MEDLINE and PubMED databases 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 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.

This review included six clinical practice guidelines, six meta-analyses, and 28 randomized controlled trials or phase III clinical studies. Several relevant retrospective case series are also included in the discussion for this guideline, but were not considered to be strong evidence when developing the recommendations.

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. 16,17 Different recommendations may apply to pediatric patients or patients receiving treatment for hematological malignancies, such as myeloma.
RECOMMENDATIONS

The following recommendations describe clinical scenarios for which antithrombotic therapy is indicated in patients with cancer. Strong evidence (i.e., phase III clinical trials and randomized controlled trials as well as the latest [2013] American Society of Clinical Oncology [ASCO] clinical practice guideline) was used to inform the recommendations; however, in the absence of strong evidence, lower quality studies (i.e., retrospective case series) were considered only in the context of consensus opinion.

1. Although the use of antithrombotic agents is contraindicated in patients with active life-threatening bleeding, antithrombotic therapy is otherwise relatively safe and most 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** for VTE. Proximal lower extremity DVT and PE should be considered for antithrombotic therapy. Other VTE should be considered for antithrombotic therapy, based on symptoms and risk factors. In patients for whom antithrombotic therapy is not contraindicated, consider using one of the following:
   - Low molecular weight heparin (LMWH i.e., dalteparin, tinzaparin, or enoxaparin) is the treatment of choice in this setting due to decreased recurrence rates on treatment; however, if the patient has non-dialysis dependent severe kidney failure (eGFR 20-30 mL per minute), tinzaparin should be considered the agent of choice (Table 2). Administration is as follows:
     - dalteparin (200 units per kg SC per day for 1 month, then 150 units per kg SC per day)
       - The first month is dosed higher and then reduced as per the CLOT Trial.
     - enoxaparin (1 mg per kg BID or 1.5 mg per kg SC per day)
       - There is no consensus on dosage for cancer-associated thrombosis because there are no completed phase III trials in cancer patients.
     - tinzaparin (175 units per kg SC per day)
   - New oral anticoagulant agents (i.e., apixaban, dabigatran, rivaroxaban) have not yet been proven to be efficacious or safe in oncology patients.
   - Although less favored, warfarin (5-10 mg orally per day, 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 and dalteparin in randomized clinical trials. 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.
   - Patients being treated for VTE should be aware of their condition and planned treatment, informed of the signs and symptoms of DVT and PE, as well as side effects of anticoagulation therapy, and instructed to inform other health care providers that they are using antithrombotic therapy. Education should be provided by health care professionals with oncology experience.

3. **Ambulatory patient prophylaxis** for VTE. High risk outpatients (i.e., patients with a risk factor score of three or more; see Figure 1) may 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:
  o dalteparin (5,000 units SC per day)
  o enoxaparin (40 mg SC per day or 30 mg BID)
  o tinzaparin (4,500 units SC per day or 75 units per kg per day)

• Prophylactic anticoagulation is not officially recommended for all ambulatory oncology outpatients by the most recent ASCO guidelines for anticoagulation (2013).

• Patients being considered for prophylaxis with antithrombotic therapy should be informed of their risk of VTE and the signs and symptoms of DVT and PE, as well as side effects of anticoagulation therapy (i.e., risk of bleeding).

• 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.

• The most recent ASCO guidelines for anticoagulation (2013) recommend extended prophylaxis with LMWH for up to 4 weeks postoperatively be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or additional risk factors (Table 3). 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 for VTE. Proximal lower extremity DVT and PE should be considered for antithrombotic therapy. Other VTE should be considered for antithrombotic therapy based on symptoms and risk factors.

• LMWH (i.e., dalteparin, tinzaparin, or enoxaparin) is the treatment of choice in this setting due to decreased recurrence rates on treatment; however, if the patient has severe non-dialysis dependent kidney failure (eGFR 20-30 mL per minute), tinzaparin should be considered the agent of choice (Table 2). Administration is as follows:
  o dalteparin (200 units per kg SC per day for 1 month, then 150 units per kg SC per day)
    ▪ The first month is dosed higher and then reduced as per the CLOT Trial.
  o enoxaparin (1 mg per kg BID or 1.5 mg per kg SC per day)
    ▪ There is no consensus on dosage for cancer-associated thrombosis as there are no completed phase III trials.
    ▪ For some physicians 1 mg BID or 1.5 mg per kg per day is acceptable.\(^ {10,19}\)
  o tinzaparin (175 units per kg SC per day)

• New oral anticoagulant agents (i.e., apixaban, dabigatran, rivaroxaban) have not yet been proven to be efficacious or safe in oncology patients.

• Although less favored, warfarin (5-10 mg per 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 and dalteparin in randomized clinical trials. There are no completed phase III trials comparing enoxaparin with warfarin. LMWH or UFH must 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.\textsuperscript{20,21}

- Patients being treated for VTE should be aware of their condition and planned treatment, informed of the signs and symptoms of DVT and PE, as well as side effects of anticoagulation therapy, and instructed to inform other health care providers that they are using antithrombotic therapy. Education should be provided by health care professionals with oncology experience.

- Patients scheduled for surgery, according to anticoagulation guidelines published in the Chest Journal (2012),\textsuperscript{22} should stop LMWH 24 hours prior to surgery or UFH 4-6 hours prior to surgery. 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).

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

- The recommended prophylactic antithrombotic therapy is LMWH, including any of the following:
  - dalteparin (5,000 units SC per day)
  - enoxaparin (40 mg SC per day or 30 mg BID)
  - tinzaparin (4,500 units SC per day or 75 units per kg SC per day)

- Patients being considered for prophylaxis with antithrombotic therapy should be informed of their risk of VTE and the signs and symptoms of DVT and PE, as well as side effects of anticoagulation therapy, and be provided with options to lower the risk.

- 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.** Described in Table 2 are 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. The first follow up CBC should be checked within 5-10 days of starting either LMWH or UFH to assess for heparin induced thrombocytopenia (HIT), a rare but life threatening complication of heparin-based therapy. CBC should be checked at a minimum of monthly intervals.

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. **Patient Education.** Patients and their care takers should be informed about VTE as well as about its treatment. The benefits of treatment should be weighed against risks. Patients should also be trained in self-injection with the assistance of clinic nurse. Items that should be reviewed include:

- VTE risk and options to lower the risk; review administration route (i.e., injection vs. oral medication; orals agents are currently not supported in oncology);
• symptoms of a blood clot, particularly pulmonary embolism, and what to do if one is suspected;
• purpose of anticoagulation medication;
• restrictions when on anticoagulation medication (i.e., alcohol in moderation only) and risks of using/taking anticoagulation medication (i.e., bleeding on an anticoagulant is a medical emergency);
• post-thrombotic syndrome; and
• blood clot prevention

Figure 1. Algorithm for VTE prophylaxis and treatment in patients with solid tumours.
Table 2. Recommended use of antithrombotic agents in special clinical scenarios.

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count &lt;50,000/µL (thrombocytopenia)</td>
<td>• 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. 23-27 • Use of LMWH should be made on a case-by-case basis with utmost caution if platelets &lt;50,000/µL. • LMWH should be stopped 24 hours prior to surgery. 22 • UFH should be stopped 4-6 hours prior to surgery. 22 • LMWH and UFH should not be re-started until the high-risk period is over (at physician discretion), typically at least 3 days post-surgery. 22 • Bridging anticoagulation (i.e., short-acting LMWH given for the period during which warfarin is interrupted or if the INR is outside of the therapeutic range) is recommended for patients with a mechanical heart valve or who are at high risk of recurrent VTE, but not for those at low risk. 22 • 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 (Table 3). 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. 18</td>
</tr>
<tr>
<td>Scheduled for surgery and currently taking anticoagulant therapy</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>• LMWH can be used, at the discretion of the treating physician. 18</td>
</tr>
<tr>
<td>CNS malignancy</td>
<td>• Anticoagulation is recommended for established VTE; however, careful monitoring is necessary to limit the risk of hemorrhage. 18</td>
</tr>
<tr>
<td>Inferior vena cava (IVC) filter in place</td>
<td>• 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. 28</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>• eGFR &gt;30 mL/min: use dalteparin, 27 tinzaparin, 29,30 or enoxaparin 31 • eGFR 20-30 mL/min: use tinzaparin 29,30 • eGFR &lt;20 mL/min: do not use LMWH; use unfractionated heparin plus warfarin</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (HIT)</td>
<td>• Heparin induced thrombocytopenia (HIT) occurs as the result of heparin use (e.g., UFH or LMWH). Consultation with a hematologist may be appropriate. • HIT should be investigated if the platelet count falls by ≥50%, and/or a thrombotic event occurs, on days 5-14 (inclusive) following initiation of heparin, even if the patient is no longer receiving heparin when the event has occurred. 32 • Strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, should be treated with a non-heparin agent (danaparoid, lepirudin, argatroban, fondaparinux, or bivalirudin). 32 • Strongly suspected or confirmed HIT should not be treated with warfarin until after the platelet count has substantially recovered (≥150,000/µL); warfarin should be started only with low-maintenance doses (max 5 mg) and an alternative agent should continue until the INR is therapeutic. 32 • The risk of HIT is lower with LMWH vs. UFH (RR 0.24, 95% CI 0.07-0.82, p&lt;0.02); the risk of HIT complicated by VTE is also lower with LMWH vs. UFH (RR 0.20, 95% CI 0.04-0.90, P = 0.04). 33</td>
</tr>
<tr>
<td>Obesity</td>
<td>• Dose LMWH to actual body weight, not ideal body weight. 18 • There is no evidence to suggest that a required CVC that is operational should be removed. 22 • Anticoagulation therapy for at least 3 months is recommended for patients with cancer in whom the CVC has been removed. 22 • Anticoagulation therapy for the duration of the CVC is recommended for patients with cancer in whom the CVC has not been removed. 22</td>
</tr>
<tr>
<td>Central venous catheter (CVC) with upper extremity (i.e., above the elbow) DVT</td>
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<tr>
<td>Incidental VTE</td>
<td>• Anticoagulation with LMWH is recommended. 18</td>
</tr>
<tr>
<td>Palliative care</td>
<td>• 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.</td>
</tr>
<tr>
<td>Elderly</td>
<td>• Tinzaparin may be safer in elderly patients with poor renal function. 29</td>
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</table>
DISCUSSION

Treatment for Established VTE Using Anticoagulation Therapy

Venous thromboembolism (VTE) typically presents as deep venous thrombosis (DVT) or pulmonary embolism (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. It is important to note that 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., ultrasound) and PE (i.e., PE protocol CT scan, VQ scan). Initial therapy for established VTE should be a low molecular weight heparin (LMWH).

For maintained anticoagulation, LMWH has been shown to be more effective than warfarin therapy in cancer patients on active cancer treatment. The CLOT trial, 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. 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% of the dalteparin group (27/336) 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). 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%). There are no completed phase III trials for enoxaparin.

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). A model developed by Khorana, et al. (2008) may be useful in assessing VTE risk, based on specific patient factors (Table 3). The ASCO 2013 clinical practice guideline suggests that this model is intriguing but does not endorse its use as a formal recommendation.

Table 3. Predictive model for chemotherapy-associated VTE (high risk is defined as a risk score of three or more).

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Score</th>
<th>Risk of VTE</th>
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<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas, brain)</td>
<td>2</td>
<td>Score ≥3 = 7%</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prechemotherapy platelet count ≥350,000/µL</td>
<td>1</td>
<td>Score 1-2 = 2%</td>
</tr>
<tr>
<td>Hemoglobin &lt;100g/L or use RBC growth factors</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count &gt;11,000/µL</td>
<td>1</td>
<td>Score 0 = 0.5%</td>
</tr>
<tr>
<td>Body mass index ≥35 kg/m²</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Several meta-analyses on the role of VTE prophylaxis have been performed and include patients with central venous catheters, patients undergoing neurosurgical procedures, patients with lung cancer receiving chemotherapy, and patients with cancer undergoing surgery. Data from twelve randomized
controlled trials on patients with a CVC suggested that the risk of symptomatic and asymptomatic DVT may be reduced with the use of prophylactic LMWH, versus no treatment; however statistical significance was not reached (RR=0.54; 95% CI 0.28–1.05 and RR=0.81; 95% CI 0.64–1.02, respectively). Moreover, there was no significant reduction in the risk of mortality (RR=0.85; 95% CI 0.53–1.37) between patients treated with prophylactic LMWH and those who received no treatment. 38

Among patients undergoing neurosurgery, the use of prophylactic LMWH was shown to reduce the risk of DVT by 40% versus no treatment (RR=0.60; 95% CI 0.44–0.81) in an analysis of 18 randomized controlled trials. 39 Data from patients with lung cancer receiving chemotherapy, who also received prophylactic LMWH and unfractionated heparin; LMWH = low molecular weight heparin; CVC = central venous catheter

The type of prophylactic anticoagulant agent used in patients with cancer may be of less importance. Data from 14 randomized controlled trials on patients with cancer undergoing surgery, comparing prophylactic LMWH and UFH showed a no significant reductions in the risk of mortality (RR=0.58; 95% CI 0.31–0.95). 39 Symptomatic VTE was also reduced by 42% with the use of prophylactic LMWH but not significantly (RR=0.58; 95% CI 0.28–1.06).37 Table 4 provides a brief summary of the evidence.

### Table 4. Randomized controlled trials on the use of anticoagulation agents for venous thromboembolism prophylaxis.

<table>
<thead>
<tr>
<th>Author Year (Trial)</th>
<th>Phase</th>
<th>Agent</th>
<th>Control</th>
<th>Patient Characteristics</th>
<th>Events (VTE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agnelli G 2012 (SAVEONCOC)45</td>
<td>III</td>
<td>semuloparin</td>
<td>placebo</td>
<td>solid tumours, pre-chemo (n=3216)</td>
<td>1.2% 3.4%</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Maraveyas A 2012 (FRAGEM)43</td>
<td>III</td>
<td>dalteparin</td>
<td>control</td>
<td>pancreatic tumours (n=123)</td>
<td>12.0% 28.0%</td>
<td>p=.04</td>
</tr>
<tr>
<td>Levine MN 2012 (ADVOCATE)44</td>
<td>II</td>
<td>apixaban</td>
<td>placebo</td>
<td>solid tumours, chemo (n=125)</td>
<td>0.0% 10.0%</td>
<td></td>
</tr>
<tr>
<td>Haas S 2012 (TOPIC-2)49</td>
<td>III</td>
<td>certoparin</td>
<td>placebo</td>
<td>NSCLC, chemo (n=353)</td>
<td>4.5% 8.3%</td>
<td></td>
</tr>
<tr>
<td>Larocca A 2010 (LIFENOX)47</td>
<td>III</td>
<td>enoxaparin</td>
<td>aspirin</td>
<td>MM, lenalidomide (n=342)</td>
<td>1.2% 2.3%</td>
<td>p=.45</td>
</tr>
<tr>
<td>Kakkar AK 2011 (LIFENOX)47</td>
<td>III</td>
<td>enoxaparin</td>
<td>control</td>
<td>acutely ill (n=8307; 5.9% cancer)</td>
<td>0.2% 0.1%</td>
<td></td>
</tr>
<tr>
<td>Palumbo A 2011 (CERTIFY)49</td>
<td>III</td>
<td>enoxaparin</td>
<td>control</td>
<td>MM, thalidomide (n=667)</td>
<td>3.2% 8.2%</td>
<td>p=.02</td>
</tr>
<tr>
<td>Haas S 2011 (CERTIFY)49</td>
<td>III</td>
<td>certoparin</td>
<td>UFH</td>
<td>solid tumours (n=274)</td>
<td>4.5% 6.0%</td>
<td></td>
</tr>
<tr>
<td>Kessler 2011 (CERTIFY)49</td>
<td>III</td>
<td>LMWH</td>
<td>control</td>
<td>MM, chemo (n=258)</td>
<td>3.4% 12.9%</td>
<td>p=.007</td>
</tr>
<tr>
<td>Agnelli G 2010 (PROTECHT)51</td>
<td>III</td>
<td>nadroparin</td>
<td>placebo</td>
<td>solid tumours, chemo (n=1168)</td>
<td>2.0% 3.9%</td>
<td>p=.02</td>
</tr>
<tr>
<td>Kakkar V 2010 (CANBESURE)52</td>
<td>III</td>
<td>bemiparin</td>
<td>placebo</td>
<td>cancer surgery (n=625)</td>
<td>0.8% 4.6%</td>
<td>p=.01</td>
</tr>
<tr>
<td>Perry 2010 (PRODIGE)53</td>
<td>III</td>
<td>dalteparin</td>
<td>control</td>
<td>glioma, no chemo (n=186)</td>
<td>9.1% 14.9%</td>
<td>p=.29</td>
</tr>
<tr>
<td>Hull RD 2010 (EXCLAIM)54</td>
<td>III</td>
<td>enoxaparin</td>
<td>placebo</td>
<td>acutely ill (n=5963; 1.6% cancer)</td>
<td>2.5% 4.0%</td>
<td></td>
</tr>
<tr>
<td>Riess H 2009 (CONKO)55</td>
<td>III</td>
<td>enoxaparin</td>
<td>placebo</td>
<td>pancreatic tumours (n=540)</td>
<td>5.0% 14.5%</td>
<td>p&lt;.01</td>
</tr>
<tr>
<td>Young AM 2009</td>
<td>III</td>
<td>warfarin</td>
<td>control</td>
<td>cancer, chemo, CVC (n=1590)</td>
<td>6.0% 6.0%</td>
<td>p=.98</td>
</tr>
<tr>
<td>Karthaus M 2006</td>
<td>III</td>
<td>dalteparin</td>
<td>placebo</td>
<td>cancer, chemo (n=439)</td>
<td>3.7% 3.4%</td>
<td>p=.88</td>
</tr>
<tr>
<td>Simonneau G 2006</td>
<td>III</td>
<td>nadroparin</td>
<td>enoxaparin</td>
<td>cancer surgery (n=1288)</td>
<td>15.9% 12.6%</td>
<td></td>
</tr>
<tr>
<td>Verso M 2005</td>
<td>III</td>
<td>enoxaparin</td>
<td>control</td>
<td>cancer, CVC (n=321)</td>
<td>14.1% 18.0%</td>
<td></td>
</tr>
<tr>
<td>Couban S 2005</td>
<td>III</td>
<td>warfarin</td>
<td>control</td>
<td>cancer, CVC (n=255)</td>
<td>1.6% 4.0%</td>
<td></td>
</tr>
<tr>
<td>Abdelkefi A 2004</td>
<td>III</td>
<td>LD-UFH</td>
<td>placebo</td>
<td>hematological cancer (n=128)</td>
<td>1.5% 12.6%</td>
<td>p=.03</td>
</tr>
<tr>
<td>Kakkar AK 2004 (FAMOUS)63</td>
<td>III</td>
<td>dalteparin</td>
<td>control</td>
<td>solid tumours (n=385)</td>
<td>2.4% 3.3%</td>
<td></td>
</tr>
<tr>
<td>Minnema MC 2004</td>
<td>III</td>
<td>nadroparin</td>
<td>control</td>
<td>MM (n=412)</td>
<td>5.0% 9.0%</td>
<td>p=.15</td>
</tr>
<tr>
<td>Lee AY 2003</td>
<td>III</td>
<td>dalteparin</td>
<td>control</td>
<td>cancer, previous VTE (n=672)</td>
<td>8.0% 15.8%</td>
<td>p=.002</td>
</tr>
<tr>
<td>Mismetti P 2003</td>
<td>III</td>
<td>nadroparin</td>
<td>control</td>
<td>cancer, chemo, CVC (n=59)</td>
<td>28.6% 16.7%</td>
<td>p=.48</td>
</tr>
</tbody>
</table>

NOTE: 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

The type of prophylactic anticoagulant agent used in patients with cancer may be of less importance. Data from 14 randomized controlled trials on patients with cancer undergoing surgery, comparing prophylactic LMWH and UFH showed a no significant reductions in the risk of mortality (RR=0.89; 95% CI 0.61–1.28) or the clinical DVT (RR=0.73; 95% CI 0.23–2.28). 41 A subsequent randomized controlled trial (i.e., CERTIFY trial) comparing prophylactic LMWH (certoparin, 3,000 units per day) with UFH (5,000 units every 8 hours)
in elderly (e.g., 70 years or older) acutely ill patients with cancer (n=274) found no difference in the odds of a thromboembolic event (i.e., DVT, symptomatic PE, VTE-related death) between these two agents (OR=0.73; 95% CI 0.23-2.39). 49

Anticoagulation Therapy and Survival

This guideline did not look specifically at the effect of prophylactic antithrombotic therapy on survival; however, the literature on this topic seems to favor antithrombotic therapy. A meta-analysis of 14 studies comparing UFH, LMWH, and warfarin with control (i.e., no treatment) in patients without VTE showed a significantly lower risk of mortality with anticoagulants overall (RR=0.91; 95% CI 0.85-0.97; p=.003); however, the effect for individual types of anticoagulants was only significant for LMWH (RR=0.88; 95% CI 0.79-0.98; p=0.015), not for UFH (RR=0.86; 95% CI 0.72-1.03; p=.095) nor for warfarin (RR=0.94; 95% CI 0.85-1.04; p=.239). 66 Despite the observed benefit of anticoagulants, the risk of major bleeding complications in patients without VTE was increased with anticoagulant users versus controls (RR=2.60; 95% CI 1.94-3.45; p=0.000). 67 Current guideline recommendations do not support the use of anticoagulants to improve survival in patients with cancer without VTE, but do support the participation of patients with cancer in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies. 18

Contraindications and Side Effects of Anticoagulation Therapy

Treatment with antithrombotic therapy is contraindicated in patients with life-threatening bleeding or severe thrombocytopenia. Acute VTE carries a significant risk of early recurrence/extension/embolization in the absence of anticoagulation even in thrombocytopenic patients though. Thus anticoagulant options for those with a platelet count <50,000µL should be reviewed with a specialist and close patient monitoring is required on or off anticoagulation. Decisions on 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. 67 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% versus 1.7%). 39 As compared to UFH, the risk of major bleeding with LMWH is not significantly different (RR=0.95; 95% CI 0.51-1.77). 43 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%). 29,47,58

The use of LMWH should be cautioned in patients with renal impairment (i.e., creatinine clearance ≤30 mL/min). 18 Accumulation of LMWH can occur in patients with impaired renal function as a result of reduced excretion; this results in an increased risk of bleeding. However, data suggest that not all LMWH drugs carry the same risk of accumulation; in fact, higher molecular weight LMWH drugs may not be cleared renally at all, but rather through cellular removal. Of the available LMWHs, tinzaparin has the highest average molecular weight at 6,500 Da, as compared to enoxaparin at 4,400 Da. 68 Among patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) who received therapeutic enoxaparin (1 mg/kg, every 12 hours or 1.5 mg/kg once daily) for 6 months, clinically relevant bleeding occurred in 22% (13/59) versus in 6% (6/105) in patients with normal renal function versus (OR 3.9 (95% CI, 0.97-15.6; p=.055). 69 Therapeutic and prophylactic doses of tinzaparin have been shown to be a safer alternative to other LMWH options in patients with renal insufficiency (i.e., serum creatinine ≥300 µmol/L and creatinine clearance >20 or creatinine clearance between 20-30 mL/min). 29,70,71 The Chest Journal guidelines reference data showing that tinzaparin clearance was not correlated with creatinine clearance, even at a rate as low as 20 mL/min. 29,32,72 Data for dalteparin use in severe renal dysfunction are limited.
The DIRECT Study included critically ill patients (N=138) with a creatinine clearance <30 mL/min given dalteparin (5,000 IU daily) in the prophylactic setting. Bioaccumulation (i.e., anti-Xa level >0.40 IU/mL) occurred in no patients (0%; 95% CI 0%-3.0%) and the median (IQR) trough anti-Xa level was undetectable (<0.10 IU/mL). Dose adjustments according to anti-Xa are recommended for dalteparin if used in patients with renal insufficiency.

**Challenges with Using Low Molecular Weight Heparin**

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

*Liver cirrhosis.* A recent randomized controlled trial in patients with advanced cirrhosis showed that, as compared to observation, enoxaparin was associated with less liver decompensation (38.2% vs. 83.0%; p<.0001) with no hemorrhagic events reported. 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.

*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. 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. 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.

*Patients scheduled for surgery.* Because of the bleeding risk associated with surgery, caution must be used in patients already taking anticoagulation therapy. According to anticoagulation guidelines published in the Chest Journal, patients scheduled for surgery should stop LMWH 24 hours prior to surgery or UFH 4-6 hours prior to surgery. In patients undergoing a high-bleeding risk surgery, therapeutic LMWH or UFH should not be re-started until the high-risk period is over at physician discretion, typically at least 3 days post-surgery. DVT prophylaxis (low dose LMWH or UFH) can be started earlier if hemodynamically stable (often on post-operative day 1). In patients undergoing a low-bleeding risk surgery (i.e., dermatological, ophthalmological, dental), anticoagulation therapy can usually be continued through the procedure. If anticoagulation is discontinued, therapeutic anticoagulation with LMWH should be resumed within 24 hours after the procedure if there is adequate hemostasis. In patients not currently taking anticoagulation therapy, ASCO guidelines recommend that patients undergoing major cancer surgery receive prophylaxis starting before surgery and continuing for up to four weeks in high-risk patients. The American College of Chest Physicians evidence-based clinical practice guidelines also recommend that high-risk patients undergoing abdominal or pelvic cancer surgery receive extended prophylaxis for up to four weeks. 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). 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 3 major and 28 minor bleeding incidents, the low-molecular-weight heparin was a risk factor. 

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 the International Clinical Practice Guidelines suggest that in cancer patients with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50,000/µL and there is no evidence of bleeding. Acute VTE carries a significant risk of early recurrence/extension/embolization in the absence of anticoagulation even in thrombocytopenic patients though. Thus anticoagulant options for those with a platelet count <50,000/µL should be reviewed with a specialist and close patient monitoring is required on or off anticoagulation. Decisions on treatment and dosage should be made on a case-by-case basis with the utmost caution. The ASCO guidelines (2013) do not recommend anticoagulant prophylaxis or therapy in patients with a platelet count <50,000/µL. Only the monograph for dalteparin provides specific dose reduction instructions: “in the case of chemotherapy-induced thrombocytopenia with platelet counts <50,000/mm3, dalteparin should be interrupted until the platelet count recovers above 50,000/mm³; for platelet counts between 50,000 and 100,000/mm³, dalteparin should be reduced by 17% to 33% of the initial dose.”

**Heparin-Induced Thrombocytopenia (HIT).** HIT is thrombocytopenia that occurs as the result of heparin use. The American College of Chest Physicians recommends that HIT be investigated if the platelet count falls by ≥50%, and/or a thrombotic event occurs, between days 5 and 14 (inclusive) following initiation of heparin. Strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, should be treated with an alternative, nonheparin anticoagulant (danaparoid, lepirudin, argatroban, fondaparinux, or bivalirudin). After the platelet count has substantially recovered (usually, to at least 150 x 10⁹/L), warfarin can be started and with the nonheparin anticoagulation used as bridging therapy until the INR is therapeutic. The British Committee for Standards in Haematology (Watson 2012) has put forth recommendations that are concordant with those of the American College of Chest Physicians. 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. A pharmacodynamic study looking at tinzaparin weight-adjusted dosing in obese patients (101-165 kg; 26-61 kg/m2) 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.

**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. Incidental VTE may be treated the same way symptomatic VTE would be treated (see recommendations).

**MAINTENANCE**

A formal review of the guideline is scheduled to be conducted in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
DISSEMINATION

- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHS</td>
<td>Alberta Health Services</td>
</tr>
<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>BID</td>
<td>twice per day</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CVC</td>
<td>central venous catheter</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>LMWH</td>
<td>low molecular weight heparin</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
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</table>

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Tumour Program in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Although some members of the Alberta Provincial Tumour Program are involved in research funded by industry or have other such potential conflicts of interest, the guideline writers are satisfied it was developed in an unbiased manner.

REFERENCES

6. Carrier M, Easaw J, Shivakumar S. VTE Treatment and Secondary prophylaxis in Ambulatory Oncology Patients. VTE Oncology Simplified.


