OBJECTIVE:
To assist health care professionals in the management of cancer-associated thrombosis (CAT).

BACKGROUND:
Low molecular weight heparin (LMWH) is the treatment of choice in patients with CAT because it offers superior efficacy over warfarin. Other non-anticoagulant effects of LMWH (e.g. anti-inflammatory properties) may also make it more effective than warfarin in CAT. The major barriers for LMWH use are drug cost and discomfort of daily injections; however, studies have shown that LMWH is well accepted by patients while warfarin is associated with a reduced quality of life. Target-specific oral anticoagulants, such as apixaban, dabigatran and rivaroxaban, are not recommended for use in this patient population due to the paucity of data specifically in this patient group, potential drug interactions with chemotherapeutic agents, unpredictable GI absorption in those with nausea, vomiting and diarrhea, frequent hepatic and renal impairment, and lack of proven reversal agents. In cancer patients, these drugs have not yet been compared with LMWH or warfarin.

MANAGEMENT APPROACHES TO DVT AND/OR PE IN CANCER PATIENTS:
Monotherapy with LMWH should be started with the diagnosis of DVT or PE in a patient with active cancer. Therapeutic dosing varies depending on the specific LMWH. Of note, only dalteparin has regulatory approval in Canada for extended treatment of cancer-associated thrombosis. Baseline CBC and renal function should be checked prior to starting LMWH. In patients with active bleeding or severe thrombocytopenia (platelet count <50 x 10^9/L) in whom anticoagulation can be dangerous, urgent referral to a hematologist or thrombosis expert for management is recommended. Insertion of a vena cava filter is not recommended for recurrent thrombosis in patients receiving therapeutic anticoagulation.

LMWH DOsing:
- Dalteparin 200 U/kg daily, rounding up to the nearest prefilled syringe (available in doses of 10,000 U, 12,500 U, 15,000 U, and 18,000 U) for the first month; then continue at ~150 U/kg daily. Tinzaparin 175 IU/kg daily and enoxaparin 1 mg/kg twice daily are generally given at full doses for the duration of treatment.
- In patients weighing more than 90 kg, twice daily dosing of dalteparin or use of multi-dose vials (25,000 U/mL concentration in 3.8 mL vials). No capping of the dose in obese patients is recommended.
• In patients with severe renal insufficiency (creatinine clearance [CrCl] <30 mL/min), LMWH is generally avoided because of its dependence on renal clearance. However, it is possible to use LMWH if measurement of anti-Xa levels is available to guide dose adjustment. Dose reduction is necessary if the trough anti-Xa level is >0.4 IU/mL. If anti-Xa levels are not readily available, then warfarin is preferred.

**Duration of Therapy:**

Patients should receive anticoagulation for a minimum of 3 to 6 months. At that time, continued anticoagulation is recommended if the patient: 1) is receiving systemic chemotherapy; 2) has metastatic disease; 3) has progressive or relapsed disease; or 4) has other ongoing risk factors that increase the risk of recurrent thrombosis (e.g. central venous catheter). Thereafter, reassessment should be done every 3 – 6 months. Even after 6 months of treatment, the risk of recurrent thrombosis is high at ~0.7%/month while on LMWH therapy (so the risk is expected to be much higher if no anticoagulation was used). Bleeding risk also remains increased throughout anticoagulation. These risks must be considered along with patient preference, quality of life and life expectancy when making a decision about continuation of anticoagulation.

**Monitoring:**

Patient weight, CBC and renal function should be checked at least every 3 – 6 months. Laboratory monitoring with anti-Xa levels is not routinely required. Heparin-induced thrombocytopenia is uncommon, occurring in <0.5% of patients who are receiving long-term, full-dose LMWH. Injection site bruising and hematomas can be minimized by applying gentle pressure to the injection site for 2-5 minutes after an injection.

**Special Considerations:**

**Perioperative management:** Cancer patients are at higher risk for developing post-operative VTE. Stopping LMWH is not necessary for procedures associated with a very low risk of bleeding, such as skin biopsy. For major surgery or other procedures associated with an increased bleeding risk, the last injection of therapeutic-dose LMWH should NOT be given within 24 hours before the procedure. Provided that hemostasis is achieved, a prophylactic dose of LMWH can be restarted 12-24 hours after the procedure. If there is no bleeding, then the dose can be escalated towards the therapeutic dose over the next 24-72 hours. For procedures or surgeries associated with a very high risk of bleeding (e.g. transurethral resection of the prostate), it is important to be conservative when reintroducing LMWH to avoid causing serious bleeding that will lead to prolonged withholding of anticoagulation.

**Thrombocytopenia:** In patients who develop thrombocytopenia, full-dose LMWH can be continued unless the platelet count is <50 x 10^9/L. Half-dose LMWH is recommended for patients with a platelet count between 20 and 50 x 10^9/L. For patients with a platelet count <20 x10^9/L, anticoagulants are usually withheld until the platelet count increases.

**Active bleeding:** Hold LMWH until the bleeding source is treated or bleeding stops. If bleeding was not in a critical site or came from a local lesion that has been treated, then LMWH can be
reintroduced once bleeding stops. Avoid insertion of an IVC filter if bleeding is expected to be transient.

**Catheter-related thrombosis:** Anticoagulant therapy generally involves the same regimen as for DVT/PE using LMWH alone or transition to warfarin for long-term treatment. Treatment should continue for a minimum of 3 months and as long as the catheter remains in place (see the Clinical Guide: Central Venous Catheter-Related Venous Thrombosis).

**Incidental thrombosis:** Incidental thrombosis is common during imaging of the chest or abdomen to assess for cancer recurrence or response to cancer treatment. Patients may or may not have symptoms consistent with thrombosis. Referral to or discussion with a specialist is recommended to help guide whether anticoagulation is warranted.

- **Pulmonary embolism:** involvement of segmental or more proximal pulmonary arteries warrants anticoagulant therapy with the same treatment regimen as for symptomatic thrombosis. There may be exceptions when anticoagulation is not warranted (e.g. isolated subsegmental pulmonary embolism).
- **Portal or splenic vein thrombosis:** asymptomatic portal vein thrombosis may not require treatment, especially if there are signs that it is chronic (e.g. cavernous transformation). Symptomatic events should be treated.
- **Mesenteric, renal, cerebral vein thrombosis:** such thrombi warrant anticoagulant therapy with the same treatment regimen as for symptomatic thrombosis.

**Cancer-associated thrombosis in children:** Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and an adult or pediatric hematologist is recommended.

**OTHER RELEVANT GUIDES:**
- Central Venous Catheter-Related Venous Thrombosis
- Heparin-Induced Thrombocytopenia (HIT)
- Pediatric Thrombosis
- Unfractionated Heparin and Low-molecular-weight Heparin
- Vena Cava Filter

**RELEVANT PUBLICATION:**

**REFERENCES:**


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Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.