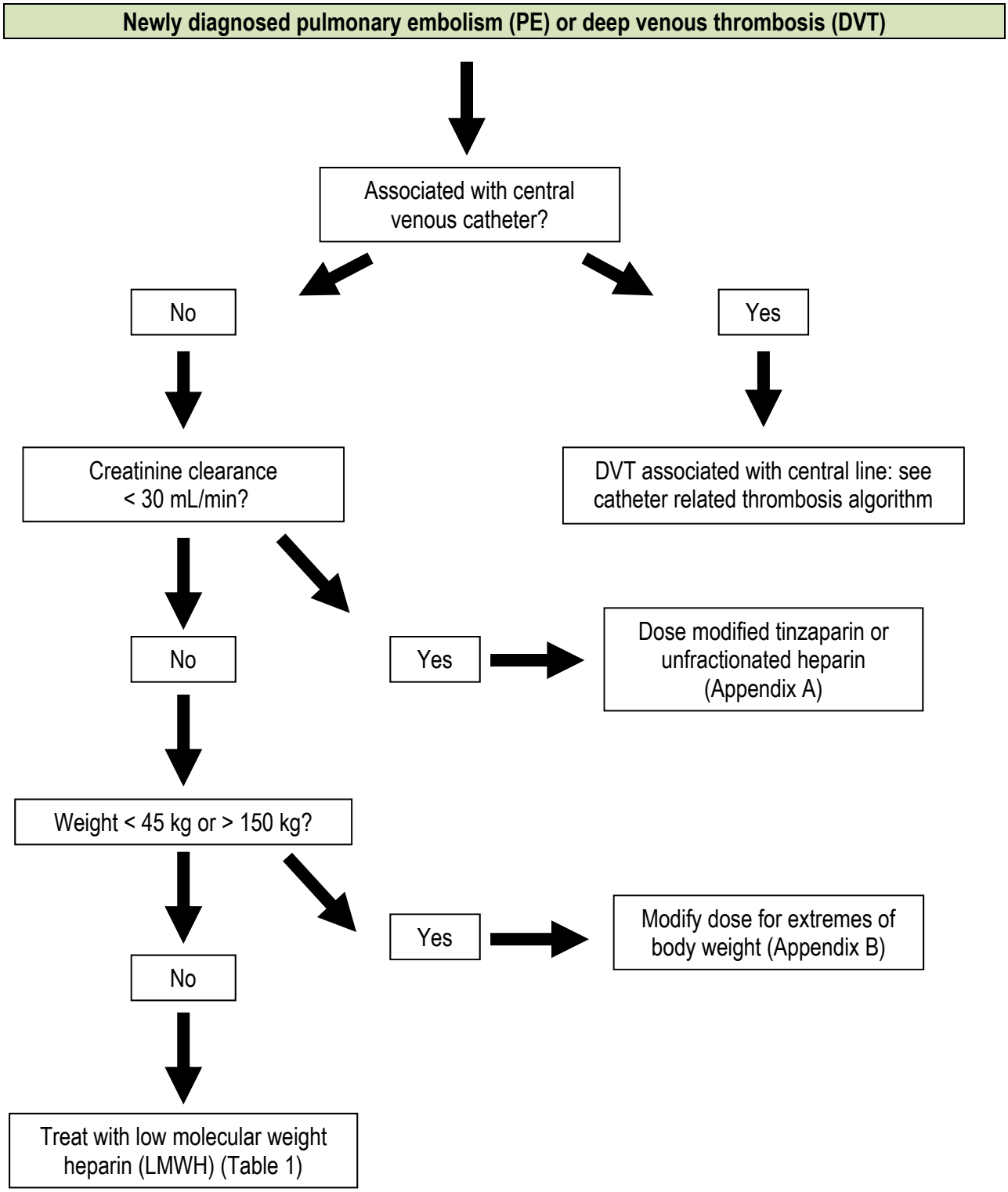
Practice Guidelines for the Management and Prophylaxis of Thrombosis in Cancer Patients



Recommendations for initial treatment of established VTE

1. Low molecular weight heparin (LMWH) is recommended for treatment of established VTE in cancer patients (Table 1) who have no contraindications to systemic anticoagulation (Table 2).
2. The use of vitamin K antagonists (VKAs) are not recommended in this patient population due to inferior efficacy.
3. The use of new oral anticoagulants is not recommended in this patient population due to lack of data.

Table 1: Preparations and dosage of anticoagulation for initial treatment

LMWH	Dosage	Level of Evidence
Dalteparin	200 IU/kg SC once daily	Excellent: recommended for use in this population[1]
Tinzaparin	175 IU/kg SC once daily	Very good: recommended for use in this population[2]
Enoxaparin	1 mg/kg SC twice daily	Limited: no specific trial showing benefit in this population
Unfractionated heparin	As per protocol	Based on historical data

[1]Lee et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003 Jul 10;349(2):146-53.
[2]Hull et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006 Dec;119(12):1062-72.

Table 2: Relative contraindications to thromboprophylactic or therapeutic anticoagulation therapy from the National Comprehensive Cancer Network (NCCN)

- Recent central nervous system bleed, intracranial or spinal lesion at high risk for bleeding
- Active major bleeding requiring blood transfusion or chronic clinically significant bleeding
- Thrombocytopenia (platelets < 50 x 10^9/L)
- Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)
- Recent major operation at high risk for bleeding
- Underlying coagulopathy due to clotting factor abnormalities, elevated prothrombin time (PT/INR) or activated partial thromboplastin time (aPTT), excluding lupus inhibitors
- Spinal anesthesia or lumbar puncture
- High risk for falls

Table 3: Availability and cost of out-patient pre-loaded syringes and multi-use vials

LMWH	Dosage Form	Cost/syringe	Example Cost for 1 Month (34 days) as of May 2013*
Dalteparin (Fragmin®)	***Preload syringe***		
	2,500 units/0.2 mL	$5.58	
	5,000 units/0.2 mL	$40.14	
	7,500 units/0.3 mL	$40.14	15,000 units once daily = $1394.61
	10,000 units/0.4 mL	$40.14	
	12,500 units/0.5 mL	$40.14	
	15,000 units/0.6 mL	$40.14	
	18,000 units/0.72 mL	$40.14	
	Single use vial		
	10,000 units/mL solution 1 mL vial	$17.61	15,000 units once daily = $927.96
	Multi use vial		
	25,000 units/mL solution 3.8 mL vial	$167.24	15,000 units once daily= $927.66
Tinzaparin (Innohep®)	***Preload syringe***		
	2,500 units/0.25 mL	$7.78	
	3,500 units/0.35 mL	$7.78	
	4,500 units/0.45 mL	$7.78	
	10,000 units/0.5 mL	$32.19	14,000 units once daily = $1124.31
	14,000 units/0.7 mL	$32.19	
	18,000 units/0.9 mL	$32.19	
	Multi use vial		
	10,000 units/mL solution 2 mL vial	$34.72	14,000 units once daily = $856.19
	20,000 units/mL solution 2 mL vial	$70.53	14,000 units once daily = $869.16
Enoxaparin (Lovenox®)	***Preload syringe***		
	30 mg/0.3 mL	$6.72	
	40 mg/0.4 mL	$22.25	
	60 mg/0.6 mL	$22.25	80 mg twice daily = $1542.85
	80 mg/0.8 mL	$22.25	120 mg once daily = $1164.43
	100 mg/1 mL	$22.25	
	120 mg/0.8 mL	$33.37	
	150 mg/1 mL	$33.37	
	Multi use vial		
	100 mg/mL solution 3 mL vial	$66.73	80 mg twice daily = $1239.89 120 mg once daily = $937.38
*** Examples using a therapeutic dosage and weight of 75-80kg**			

Recommendations for initial treatment in patients with established VTE and special circumstances

Renal impairment

1. Consider hematology consult in patients with creatinine clearance < 30 mL/hour due to complexity of monitoring and potential complications. Suggested dosing and monitoring guidelines can be found in Appendix A.
2. Tinzaparin can be used for patients with creatinine clearance > 20 mL/hour at regular dosing (175 IU/kg sub-cu once daily) based on clinical data.
3. Unfractionated heparin can be offered to in-patients with renal impairment (creatinine clearance < 30 mL/hour) as per pharmacy provided VTE protocols with aPTT monitoring.
4. Enoxaparin and dalteparin are not recommended in patients with renal impairment due to lack of clinical data.

Extremes of body weight

1. Patients with actual body weight of > 150 kg or < 45 kg require monitoring with anti-Xa levels. Consideration of hematology consultation is recommended due to complexity of monitoring and potential complications. Suggested dosing and monitoring guidelines can be found in Appendix B.

Other special circumstances

1. In patients who have a history of heparin induced thrombocytopenia (HIT) or are suspected to have HIT, fondaparinux can be used for the initial treatment of established VTE.
2. Thrombolysis in cancer patients with established VTE may only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk (for example, due to brain metastasis).
3. In the initial treatment of VTE, vena cava filters may be considered in the case of contraindication for anticoagulation or in the case of pulmonary embolism recurrence under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended and anticoagulation should be resumed when safe. Vena cava filters are not recommended for primary VTE prophylaxis in cancer patients.
4. In patients with active VTE and critically low platelets (platelets < 30 x 10^9/L), anticoagulation may be either held or platelet transfusion administered to maintain the platelet count > 30 x 10^9/L.
5. In patients receiving treatment for malignancy with non-curative intent who develop active VTE, initial treatment with unfractionated or low molecular weight heparin is recommended.

Recommendations for ongoing management of established VTE

1. LMWHs are the recommended treatment for a minimum of 6 months after diagnosis due to improved efficacy over VKAs. Recommended doses can be found in Table 1.[1]
2. Anticoagulation with LMWH or VKA may be considered beyond the initial six months for select patients after evaluation of ongoing risk factors for development of thrombosis (i.e. immobility, hormonal adjuvant therapy etc), benefit-risk ratio, tolerability and patient preference.
3. Ongoing anticoagulation is preferred in patients who continue to have active malignancies.
4. The benefit of LMWHs versus VKAs beyond six months of therapy for newly established venous thrombosis has not been proven. The continued use of LMWH beyond six months should include such factors as economic cost, quality of life (i.e. daily injections versus a pill), and the inability or ability to access monitoring (INR).
5. LMWH is contraindicated with an estimated GFR less than 20 cc per minute. The use of UH bridged to VKAs with a goal INR of 2-3 in this context is recommended.
6. There is insufficient clinical data to support the use of new oral anticoagulants in this patient population.

Treatment of VTE recurrence in cancer patients on anticoagulation

1. In the event of VTE recurrence in patients already on anticoagulation, three options can be considered:
    a. Switch from VKA to LMWH in patients on therapeutic dose of VKA.
    b. Increase in LMWH dose by 25% in patients treated with LMWH.
    c. Vena cava filter insertion in select circumstances (evidence of efficacy generally low).
2. Consideration may be given to consulting hematology in this situation.

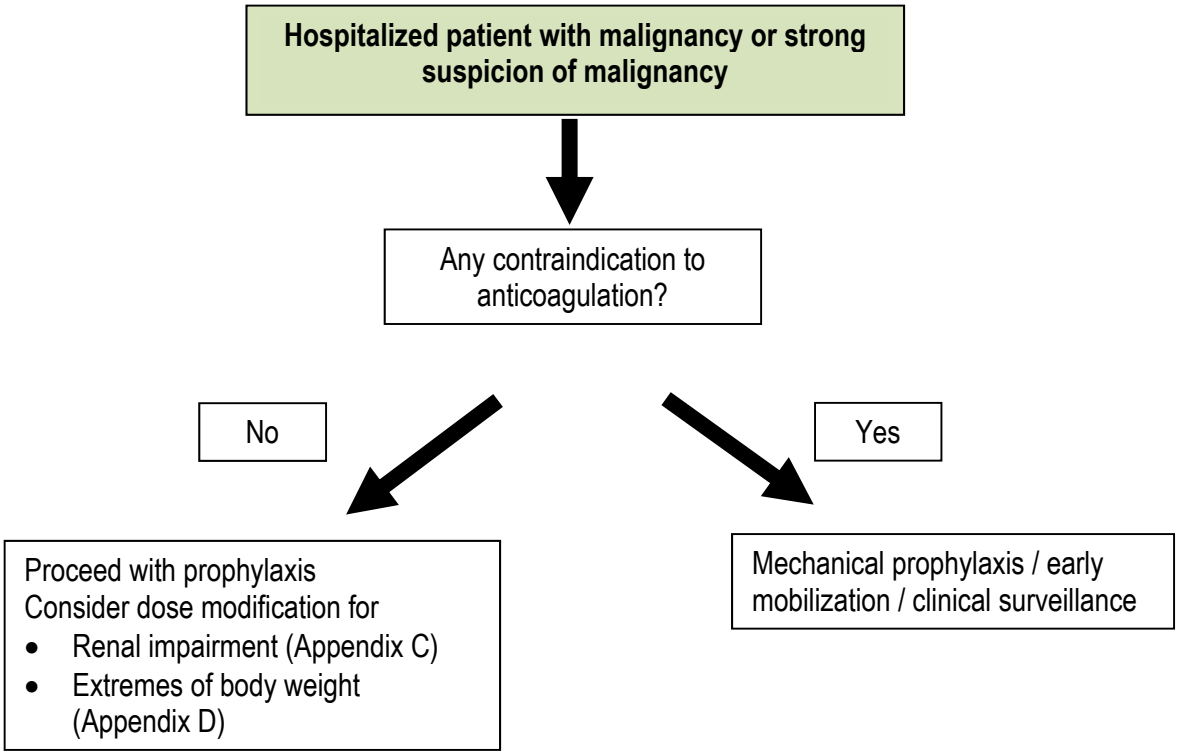
[1] To acquire EDS status, call 306-787-8744 and state that the patient has a contraindication to warfarin therapy due to active chemotherapy treatment. This status is updated on the provincial pharmacy database and will be available at the local pharmacy when the prescription for LMWH is filled.

Catheter related thrombosis (CRT)

Established catheter-related thrombosis

1. For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment with LMWH is recommended for a minimum of 3 months.
2. The central venous catheter (CVC) can be kept in place if it is functional, well positioned and not infected.
3. Close surveillance for resolution of symptoms is recommended; if symptoms persist despite appropriate treatment, the CVC may require removal.
4. It may be appropriate to extend anticoagulation beyond 3 months in the absence of recanalization and in the context of progressive disease.
5. Use of anticoagulation for routine prophylaxis of CRT is not recommended.

Prophylaxis of VTE in cancer patients



Prophylaxis of VTE in cancer patients

Prophylaxis in hospitalized patients with cancer

1. Prophylaxis is recommended for all hospitalized patients with cancer who do not have a relative contraindication to anticoagulation (Table 2).
2. Either LMWH or UFH can be used at prophylactic doses (Table 6).
3. Dose modification should be considered in renal insufficiency and extremes of body weight (Appendices C and D).

Table 6: Recommended doses of prophylactic anticoagulants

Prophylactic anticoagulant	Recommended dose
Dalteparin	5000 IU SC once daily
Enoxaparin	40 mg SC once daily or 30 mg SC twice daily
Tinzaparin	4500 IU SC once daily or 75 IU/kg SC once daily
Unfractionated heparin	5000 IU SC three times daily

Prophylaxis in cancer patients following surgery

1. Use of LMWH once a day or a low dose of UFH three times a day is recommended. There is no data allowing conclusions regarding the superiority of one type of LMWH over another (Table 5).
2. Prophylaxis should be started 12-24 h postoperatively and continued for duration of hospitalization.
3. Extended prophylaxis (4 weeks) to prevent postoperative VTE after major laparotomy in cancer patients should be considered in patients with a high VTE risk and low bleeding risk.
4. The use of LMWH for the prevention of VTE in cancer patients undergoing laparoscopic surgery may be recommended in the same way as for laparotomy.
5. Mechanical methods alone are not recommended except when pharmacological methods are contraindicated.

Prophylaxis for cancer patients not in hospital

1. In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH, low dose UFH or vitamin K antagonists.
2. In outpatients with solid tumors who have additional risk factors for VTE (Table 7) and who are at low risk of bleeding, prophylactic dose LMWH or low dose UH should be considered.
3. Routine prophylaxis is not recommended for chronically immobilized cancer patients not in hospital.

Table 7: Additional risk factors for venous thrombosis in cancer outpatients

- Previous venous thrombosis
- Immobilization
- Hormonal therapy
- Angiogenesis inhibitors [e.g. bevacizumab (Avastin®)]
- Regimens containing thalidomide, lenalidomide or pomalidomide
- Metastatic pancreatic cancer
- Metastatic lung cancer

Appendix A
Dosing and monitoring guidelines for <u>treatment</u> of VTE in patients with renal failure

Preparation	Creatinine Clearance	Dose	Monitoring	Target Level
Tinzaparin	> 20 mL/min	175 IU/Kg SC once daily	No	No
UH	10-20 mL/min	As per hospital protocol	aPTT	As per hospital protocol
Enoxaparin		Not recommended due to lack of clinical data		
Dalteparin		Not recommended due to lack of clinical data		

The preference of this committee is to use tinzaparin for patients with creatinine clearance > 20 mL/min as it is better studied in this population and does not require monitoring.

Appendix B
Dosing and monitoring guidelines for <u>treatment</u> of VTE in patients with extremes of body weight

Body Weight	Preparation /Dose	Monitoring	Target Level
Actual Body Weight > 150 kg	**UH as per VTE protocol** **Enoxaparin** 1 mg/kg SC q12h Use adjusted body weight* Minimum initial dose is 150 mg SC q12h. Do not use single-daily dosing regimen **Tinzaparin** 175 IU/kg SC if BMI > 40 kg/m^2 **Dalteparin** 200 IU/kg SC q24h	PTT An anti-Xa level should be obtained 4 hours after the 1st or 2nd dose and sent STAT to the lab	x 2 - 2.5 baseline PTT Titrate dose to maintain an anti -Xa level of 0.5 - 1 units/mL Titrate dose to maintain an anti -Xa level of 0.5 - 1 units/mL Titrate dose to maintain an anti -Xa level of 1 - 2 units/mL
Actual Body Weight < 45 kg	**UH as per VTE Protocol** **Enoxaparin** 1.5 mg/kg SC q24h actual body weight **Tinzaparin** 175 IU/kg SC q24h actual weight **Dalteparin** 200 IU/kg SC q24h actual body weight	PTT anti-Xa level should be obtained 4 hours after the 3rd AM dose and sent STAT to the lab	x 2-2.5 baseline PTT Titrate dosage to maintain an anti-Xa level of 1 - 1.5 units/mL Titrate dose to maintain an anti -Xa level of 0.5 - 1 units/mL Titrate dose to maintain an anti -Xa level of 1 - 2 units/mL

*** Adjusted body weight = Ideal BW + 0.4 (Actual BW – Ideal BW)**

Ideal BW **Men:** $50 \text{ kg} + 2.3 \text{ kg} \times \frac{\text{(height in cm - 152.4)}}{2.54}$

Women: $45.5 \text{ kg} + 2.3 \text{ kg} \times \frac{\text{(height in cm - 152.4)}}{2.54}$

Appendix C
Dosing and monitoring guidelines for prophylaxis of VTE in patients with renal failure

Preparation	Creatinine clearance (mL/min)	Dose/route
Unfractionated Heparin	< 30 mL/min	5000 IUSC q8hr
Tinzaparin	< 30 mL/min	4500 IU SC once daily
Dalteparin	< 30 mL/min	2500-5000 IU SC once daily
Enoxaparin	< 30 mL/min	40 mg SC once daily (Note: limited data to support use in this population)

Appendix D
Dosing and monitoring guidelines for prophylaxis of VTE in patients with extremes of body weight

Preparation	Body Weight	Dose/Route	Monitoring	Target
UH	< 45 kg	5000 units SC tid	No	No
	>150 kg	5000 IU SC q8h	No	No
Enoxaparin	Actual Body Weight < 45 kg	40 mg SC q24h	anti-Xa level should be obtained 4 hours after the 7th AM dose and sent STAT to the lab	Titrate dosage to maintain anti-Xa level of < 0.5 units/mL
	BMI > 40 kg/m^2	40 mg SC q12h	No	No
Tinzaparin	< 45 or > 150 kg	4500 IU SC q24h	No	No
Dalteparin	Actual Body Weight < 50 kg	5000 IU SC q24h	anti-Xa level should be obtained 4 hours after the 7th AM dose and sent STAT to the lab	Titrate dosage to maintain anti-Xa level of < 0.4 units/mL
	BMI > 40 kg/m^2 Weight >150 kg	5000 IU SC q12h 7500 IU SC q12h	No anti-Xa level should be obtained 4 hours after the 7th AM dose and sent STAT to the lab	No Titrate dosage to maintain anti-Xa level of < 0.4 units/mL