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PRACTICE GUIDELINE

Evidence-based guidance on venous thromboembolism in patients with solid tumours

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ABSTRACT

Venous thromboembolism (VTE) is a serious, life-threatening complication of cancer. Anticoagulation therapy such as low molecular weight heparin (LMWH) has been shown to treat and prevent VTE. Cancer therapy is often complex and ongoing, making the management of VTE less straightforward in patients with cancer. There are no published Canadian guidelines available to suggest appropriate strategies for the management of VTE in patients with solid tumours. We therefore aimed to develop a clear, evidence-based guideline on this topic.

A systematic review of clinical trials and meta-analyses published between 2002 and 2013 in PubMed was conducted. Reference lists were handsearched for additional publications. The National Guidelines Clearinghouse was searched for relevant guidelines. Recommendations were developed based on the best available evidence.

In patients with solid tumours, LMWH is recommended for those with established VTE and for those without established VTE but with a high risk for developing VTE. Options for LMWH include dalteparin, enoxaparin, and tinzaparin. No one agent can be recommended over another, but in the setting of renal insufficiency, tinzaparin is preferred. Unfractionated heparin can be used under select circumstances only (that is, when rapid clearance of the anticoagulant is desired). The most common adverse event is bleeding, but major events are rare, and with appropriate follow-up care, bleeding can be monitored and appropriately managed.

KEY WORDS

Anticoagulation, low molecular weight heparin, venous thromboembolism, pulmonary embolism, deep-vein thrombosis, solid tumours, clinical practice guidelines, systematic reviews

1. INTRODUCTION

Venous thromboembolism (VTE) is a vascular disorder that includes deep-vein thrombosis (DVT) and pulmonary embolism (PE). Deep-vein thrombosis is characterized by a blood clot in the deep veins, typically in the legs, but also in the arms or pelvis; PE is characterized by a blood clot in an artery of the lungs.

Patients with cancer carry an increased risk of developing VTE because of tumour- and treatment-mediated hypercoagulability[1–4]. Clinical risk factors for VTE in cancer include the primary site of cancer (highest risks include brain, pancreas, stomach, lung, colorectal, gynecologic, kidney, lymphoma, myeloproliferative, and metastatic tumours), use of systemic therapy (chemotherapy, erythropoiesis-stimulating agents, exogenous estrogens, and antiangiogenesis therapies), recent surgery, limited mobility, and hospitalization[1,5]. The use of chemotherapy carries a relative risk that is higher by a factor of 6.5 than that for the general population[3]. In a meta-analysis of 38 cohort studies, the overall risk of VTE in patients with cancer was found to be greater by more than a factor of 5 in the high-risk patients—that is, those with metastatic disease or undergoing high-risk treatments—than in the average-risk patients[4]. Several patient-related, cancer-related, and treatment-related factors can adversely affect the risk of developing cancer-associated VTE (Table I).

Venous thromboembolism 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 higher by a factor of 4 to 8 in patients with than in those without cancer[10–13]. The strongest predictor for recurrent VTE is a previous diagnosis of VTE. Venous thromboembolism is also associated with long-term complications, including post-thrombotic syndrome and pulmonary hypertension[14].

Cancer therapy is often complex and ongoing, making the management of VTE less straightforward

TABLE I Factors associated with cancer-associated venous thromboembolism (VTE)[6]

Category	*Factors*
Patient-related	
	Increased age
	Comorbidities (infection, renal and pulmonary disease, arterial thromboembolism, VTE history, inherited prothrombotic mutations
	Obesity
	Poor performance status
Cancer-related	
	Site of primary cancer
	Stage (risk increases with higher stage)
	Comorbid conditions
	Histology
	Time since diagnosis (risk might increase during the first 3–6 months)
Treatment-related	
	Chemotherapy, antiangiogenesis agents, hormonal therapy
	Radiation therapy
	Surgery lasting 60 minutes or more
	Erythropoiesis-stimulating agents, transfusions
	Indwelling venous access
Biochemical	
	Leukocyte count > 11×10^9/L
	Hemoglobin < 100 g/L
	Platelet count > 350×10^9/L

in the treated population. Furthermore, no published Canadian guidelines are available to suggest appropriate strategies for the management of VTE in patients with solid tumours. We therefore aimed to develop a clear evidence-based guideline on this topic, specifically to provide recommendations for physicians, nurses, and other front-line staff about the prophylaxis and treatment of VTE in patients with cancer, specifically those with solid tumours, both in the inpatient and the ambulatory settings. The questions addressed were these:

- What is the standard of care for patients with solid tumours with established VTE?
- Among patients with solid tumours, who should receive prophylactic antithrombotic therapy for VTE?
- What are the most common complications associated with antithrombotic therapy use, and how should special clinical scenarios be managed?

2. METHODOLOGY

2.1 Guideline Development

The review process for this guideline was developed based on an overview from the U.K. National Institute for Health and Clinical Excellence of clinical guideline development for stakeholders, the public, and the U.K. National Health Service[15]; on Cummings and Rivara's methodology for reviewing manuscripts published in the *Archives of Pediatrics and Adolescent Medicine*[16]; and on the AGREE collaboration instrument[17]. With that methodologic foundation, the guideline recommendations were drafted by a medical oncologist from the Tom Baker Cancer Centre (Calgary, AB), a hematologist from the University of Alberta (Edmonton, AB), and a cancer research methodologist from CancerControl Alberta. The guideline was reviewed by an expert panel of medical oncologists, hematologic oncologists, a surgical oncologist, a registered nurse, and a physiotherapist, representing urban and rural centres in Alberta. The evidence base for the guideline was informed by a systematic review of the literature.

2.2 Literature Search Strategy

The PubMed database of the U.S. National Library of Medicine was searched for relevant articles published between 2002 and 2013. In addition, the American Society of Clinical Oncology (ASCO) was searched for meeting abstracts published between 2010 and 2013, and the U.S. National Guideline Clearinghouse was searched for guidelines published between 2007 and 2013. Search terms included "neoplasm" or "cancer" and "venous thromboembolism" or "thrombosis" and "thrombosis prophylaxis" or "VTE prophylaxis." Results were limited to randomized controlled trials and phase III and IV clinical trials published between 2002 and March 2013, as well as meta-analyses published between 2008 and March 2013. Trials that did not report outcomes related to the prophylaxis or treatment of VTE were excluded. Because of a lack of translation services, articles in other than the English language were also excluded from the review of the evidence.

3. RESULTS AND DISCUSSION

3.1 Results of the Literature Review

The literature review included seven clinical practice guidelines, six meta-analyses, and twenty-eight randomized controlled trials. Several relevant retrospective case series were also included in the discussion, but were not considered strong evidence when developing the recommendations. Table II presents a summary of the evidence for the use of prophylactic anticoagulation.

TABLE II Trials on the use of anticoagulation agents for venous thromboembolism (VTE) prophylaxis

Reference	*Trial name*	*Phase*	*Agent*	*Control*	*Patients*		*VTE events*		
					Characteristics	(n)	*Intervention (%)*	*Control (%)*	p *Value*
Lee and Levine, 2003[10]		III	Dalteparin	Coumarin	Cancer with previous VTE	672	8.0	15.8	0.002
Mismetti *et al.*, 2003[18]		II	Nadroparin	Warfarin	Cancer, undergoing chemotherapy with central venous catheter	59	28.6	16.7	0.48
Abdelkefi *et al.*, 2004[19]		III	Low-dose UFH	Placebo	Cancer (hematologic)	128	1.5	12.6	0.03
Kakkar *et al.*, 2004[20]	FAMOUS	III	Dalteparin	Placebo	Cancer (solid tumours)	385	2.4	3.3	
Minnema *et al.*, 2004[21]		III	Nadroparin	Control	Cancer (multiple myeloma)	412	5.0	9.0	0.15
Couban *et al.*, 2005[22]		III	Warfarin	Placebo	Cancer with central venous catheter	255	1.6	4.0	
Verso *et al.*, 2005[23]		III	Enoxaparin	Placebo	Cancer with central venous catheter	321	14.1	18.0	
Karthaus *et al.*, 2006[24]		III	Dalteparin	Placebo	Cancer, undergoing chemotherapy	439	3.7	3.4	0.88
Simonneau *et al.*, 2006[25]		III	Nadroparin	Enoxaparin	Cancer, undergoing surgery	1288	15.9	12.6	
Riess *et al.*, 2008[26] and 2009[27]	CONKO	III	Enoxaparin	Control	Cancer (pancreatic tumours)	540	5.0	14.5	<0.01
Young *et al.*, 2009[28]		III	Warfarin	Control	Cancer, undergoing chemotherapy with central venous catheter	1590	6.0	6.0	0.98
Agnelli *et al.*, 2010[29]	PROTECHT	III	Nadroparin	Placebo	Cancer (solid tumours), undergoing chemotherapy	1168	2.0	3.9	0.02
Hull *et al.*, 2010[30]	EXCLAIM	III	Enoxaparin	Placebo	Acutely ill	5963 (1.6% cancer)	2.5	4.0	
Kakkar *et al.*, 2010[31]	CANBESURE	III	Bemiparin	Placebo	Cancer undergoing surgery	625	0.8	4.6	0.01
Perry *et al.*, 2010[32]	PRODIGE	III	Dalteparin	Placebo	Cancer (glioma), no chemotherapy	186	9.1	14.9	0.29
Haas *et al.*, 2011[33]	CERTIFY	III	Certoparin	UFH	Cancer (solid tumours)	274	4.5	6.0	
Kakkar *et al.*, 2011[34]	LIFENOX	III	Enoxaparin	Placebo	Acutely ill	8307 (5.9% cancer)	0.2	0.1	
Kessler *et al.*, 2011[35]		III	LMWH	Control	Cancer (multiple myeloma),	258	3.4	12.9	0.007
Palumbo *et al.*, 2011[36]		III	Enoxaparin	Warfarin	Cancer (multiple myeloma), receiving thalidomide	667	3.2	8.2	0.02
Agnelli *et al.*, 2012[37]	SAVEONCO	III	Semuloparin	Placebo	Cancer (solid tumours), pre-chemotherapy	3216	1.2	3.4	<0.001
Haas *et al.*, 2012[38]	TOPIC-2	III	Certoparin	Placebo	Cancer (NSCLC), undergoing chemotherapy	353	4.5	8.3	
Larocca *et al.*, 2012[39]		III	Enoxaparin	Aspirin	Cancer (multiple myeloma), receiving lenalidomide	342	1.2	2.3	0.45
Levine *et al.*, 2012[40]	ADVOCATE	II	Apixaban	Placebo	Cancer (solid tumours), undergoing chemotherapy	125	0.0	10.0	
Maraveyas *et al.*, 2012[41]	FRAGEM	III	Dalteparin	Control	Cancer (pancreatic tumours)	123	12.0	28.0	0.04

NSCLC = non-small-cell lung cancer; UFH = unfractionated heparin; LMWH = low molecular weight heparin.

3.2 Discussion

3.2.1 Treatment of Established VTE in Ambulatory Patients with Solid Tumours

Venous thromboembolism typically presents as DVT or PE. The signs and symptoms of DVT include pain, edema or swelling in the limbs or upper body, persistent cramping, and erythema. The signs and symptoms of PE include, but are not limited to, chest pain, shortness of breath, hypoxia, tachycardia, and tachypnea[42]. It is important to note that none of the signs or symptoms of DVT and PE are sensitive or specific for VTE, and that the index of suspicion should be high when patients with these symptoms also have a substantial risk for VTE (such as the presence of cancer). In addition to a clinical evaluation, imaging is required to diagnose DVT (that is, ultrasonography) and PE (that is, PE-protocol computed tomography imaging, ventilation-perfusion scan)[43]. Initial therapy for established VTE in cancer patients should be a low molecular weight heparin (LMWH)[42–45].

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 (specifically, dalteparin) with daily warfarin as maintenance therapy. All patients were initially treated for 6 months with either dalteparin (200 IU/kg daily subcutaneously for 1 month and 150 IU/kg daily for 5 months) or warfarin [international normalized ratio (INR) 2–3] for 6 months. Recurrent VTE occurred in 8% (27 of 336) of the dalteparin group and 16% (53 of 336) of the warfarin group (hazard ratio: 0.48; p = 0.002). Major bleeding and any bleeding did not differ between the groups (6% vs. 4% and 14% vs. 19% respectively)[46]. The LITE trial compared tinzaparin with warfarin in patients with cancer and acute symptomatic proximal DVT (n = 200). After 12 months of follow-up, recurrent VTE occurred in 7% (7 of 100) of the tinzaparin group and in 16% (16 of 100) of the vitamin K antagonist group [relative risk (RR): 0.44; p = 0.044]. Bleeding did not differ between the groups (27% vs. 24%)[47].

3.2.2 VTE Prophylaxis in Ambulatory Patients with Solid Tumours

Prophylaxis is an important consideration in the care of patients with cancer, especially those with active risk factors (erythropoiesis stimulating-agent use, exogenous estrogen use, antiangiogenic therapy use, and recent surgery)[5,10–13]. A model developed by Khorana *et al.*[5,8] could be useful in assessing VTE risk based on specific patient factors (Table III). The ASCO clinical practice guideline suggests that the model is intriguing, but does not endorse its use as a formal recommendation[48].

TABLE III Modified Khorana predictive model[a] for chemotherapy-associated venous thromboembolism (VTE)

Patient characteristic	*Risk score*	*Risk of VTE*
Site of cancer		
Very high risk[b]	2	Score ≥ 3 = 7%
High risk	1	
Pre-chemotherapy platelet count >350×10^9/L	1	Score 1–2 = 2%
Hemoglobin < 10 g/dL or use of RBC growth factors	1	
Pre-chemotherapy leukocyte count >11×10^9/L	1	Score 0 = 0.5%
Body mass index ≥ 35 kg/m^2	1	

[a] High risk is defined as a score of 3 or more[5].
[b] Stomach, pancreas, brain.
[c] Lung, lymphoma, gynecologic, bladder, testicular.
RBC = red blood cells.

Several meta-analyses on the role of VTE prophylaxis have been performed and include patients with central venous catheters[36], patients undergoing neurosurgical procedures[33], patients with lung cancer receiving chemotherapy[35], and patients with cancer undergoing surgery[29]. Data from twelve randomized controlled trials involving patients with a central venous catheter suggest that the risk of symptomatic and asymptomatic DVT might potentially be reduced with the use of prophylactic LMWH (compared with no treatment); however, statistical significance was not reached (RR: 0.54; 95% CI: 0.28 to 1.05; and RR: 0.81; 95% CI: 0.64 to 1.02 respectively). Moreover, no significant reduction in the risk of mortality was observed between patients treated with prophylactic LMWH and those who received no treatment (RR: 0.85; 95% CI: 0.53 to 1.37)[36].

Among patients undergoing neurosurgery, the use of prophylactic LMWH (compared with no treatment) was shown, in an analysis of eighteen randomized controlled trials, to reduce the risk of DVT by 40% (RR: 0.60; 95% CI: 0.44 to 0.81)[33]. Data from patients with lung cancer receiving chemotherapy who also received prophylactic LMWH (specifically, nadroparin or certoparin) were compared with data from patients on placebo in the TOPIC-2 trial. The relative risk of thromboembolic events was reduced by 46% with LMWH (RR: 0.54; 95% CI: 0.31 to 0.95)[33]. Symptomatic VTE was also reduced by 42% with the use of prophylactic LMWH, but nonsignificantly (RR: 0.58; 95% CI: 0.28 to 1.06)[45]. Table II provides a brief summary of the evidence.

The type of prophylactic anticoagulant agent used in patients with cancer might be of less importance. Data from fourteen randomized controlled trials that compared prophylactic LMWH and unfractionated heparin (UFH) in patients with cancer

undergoing surgery showed no significant reductions in the risk of mortality (RR: 0.89; 95% CI: 0.61 to 1.28) or of clinical DVT (RR: 0.73; 95% CI: 0.23 to 2.28)[49]. A subsequent randomized controlled trial (CERTIFY) comparing prophylactic LMWH (certoparin 3000 U daily) with UFH (5000 U every 8 hours) in elderly (≥70 years) acutely ill patients with cancer (n = 274) also found no difference in the odds of a thromboembolic event (DVT, symptomatic PE, VTE-related death) between the groups (odds ratio: 0.73; 95% CI: 0.23 to 2.39)[33].

The present guideline did not look specifically at the effect of prophylactic antithrombotic therapy on survival. The literature on the topic is controversial. A meta-analysis of fourteen studies comparing UFH, LMWH, or warfarin with control (that is, no treatment) in patients without VTE showed a significantly lower overall risk of mortality with anticoagulants (RR: 0.91; 95% CI: 0.85 to 0.97; p = 0.003); however, the effect for individual types of anticoagulants was significant only for LMWH (RR: 0.88; 95% CI: 0.79 to 0.98; p = 0.015) and not for UFH (RR: 0.86; 95% CI: 0.72 to 1.03; p = 0.095) or warfarin (RR: 0.94; 95% CI: 0.85 to 1.04; p = 0.239)[50]. Despite the observed benefit of anticoagulants, the risk of major bleeding in patients without VTE was increased for anticoagulant users compared with control subjects (RR: 2.60; 95% CI: 1.94 to 3.45; p = 0.000)[51]. Current guidelines do not recommend the use of anticoagulants to improve survival in patients with cancer without VTE, but they do support the participation of patients with cancer in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies[48].

3.2.3 Contraindications and Special Considerations with Antithrombotic Therapy

Use of antithrombotic therapy is contraindicated in patients with life-threatening bleeding or severe thrombocytopenia. The ASCO guidelines do not recommend anticoagulant prophylaxis or therapy in patients with a platelet count below 50,000/μL[48]. Acute VTE carries a significant risk of early recurrence, extension, or embolization in the absence of anticoagulation even in thrombocytopenic patients. Thus, anticoagulant options for individuals with a platelet count below 50,000/μL should be reviewed with a specialist, and close patient monitoring is required. That approach is supported by recommendations from the International Society on Thrombosis and Haemostasis[52]. Decisions on treatment and dose should be made case by case 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 of data from the PROTECHT and TOPIC-2 studies, the rate of major bleeding with LMWH is only slightly greater than that with placebo (2.5% vs. 1.7%)[53]. The risk of bleeding from antithrombotic therapy must be weighed against the possible therapeutic benefits; overall, however, anticoagulant therapy appears to be safe in patients without active bleeding. Major bleeding associated with LMWH is low (<1%)[24,34,41].

The use of LMWH should be cautious in patients with renal impairment (creatinine clearance ≤ 30 mL/min)[48]. Accumulation of LMWH because of reduced excretion can occur in patients with impaired renal function; accumulation 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 might be less dependent on kidney clearance.

Of the available LMWHs, tinzaparin has the highest average molecular weight at 6500 Da, compared with enoxaparin at 4400 Da[54]. Among patients with moderate renal impairment (creatinine clearance 30–50 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 of 59); such bleeding occurred in 6% of patients (6 of 105) with normal renal function (odds ratio: 3.9; 95% CI: 0.97 to 15.6; p = 0.055)[55]. Therapeutic and prophylactic doses of tinzaparin have been shown to be a safer alternative to other LMWH options in patients with renal insufficiency (serum creatinine ≥300 μmol/L and creatinine clearance > 20 mL/min, or creatinine clearance 20–30 mL/min)[56–58]. The American College of Chest Physicians (ACCP) guidelines reference data showing that tinzaparin clearance is not correlated with creatinine clearance, even at a rate as low as 20 mL/min[58–60].

Data for dalteparin use in severe renal dysfunction are limited. The DIRECT study included critically ill patients (n = 138) with a creatinine clearance less than 30 mL/min given dalteparin (5000 IU daily) in the prophylactic setting. No patients (0%; 95% CI: 0% to 3.0%) showed bioaccumulation (that is, anti–factor Xa > 0.40 IU/mL), and the median trough anti–factor Xa concentration was undetectable (<0.10 IU/mL)[61]. Similar findings have been reported elsewhere[62].

Indications for the use of an inferior vena cava (IVC) filter include recent proximal DVT plus an absolute contraindication to anticoagulation[56,63,64]. Failure of anticoagulation, poor compliance with anticoagulation, and falls are not indications for an IVC filter. Changing or intensifying anticoagulation, appropriate patient counselling, increased patient monitoring, and interventions to reduce the bleeding risk can be explored in such situations. Inferior vena cava filters are associated with high morbidity and can increase hypercoagulability; therefore, if placement is required, the filter should be removed as soon as possible (that is, once LMWH can be started). No available data support the addition of an IVC filter to pharmacologic anticoagulation therapy[52,65]. 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 the presence or absence of a filter. Contraindications to anticoagulation include a high risk for bleeding, current bleeding, and severe thrombocytopenia[63,64].

Because of the bleeding risk associated with surgery, caution must be used in patients already taking anticoagulation therapy. According to the ACCP guidelines, patients scheduled for surgery should stop LMWH 24 hours before surgery or UFH 4–6 hours before surgery. In patients undergoing a high-bleeding-risk surgery, therapeutic doses of LMWH and UFH should not be re-started until the high-risk period for bleeding is over[66]. Prophylaxis for DVT (low-dose heparin or UFH) can be initiated earlier, often on postoperative day 1 if there is no active bleeding. In patients undergoing a low-bleeding-risk surgery (dermatologic, ophthalmologic, 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 hemostasis is adequate[56]. Postoperative VTE prophylaxis is recommended based on evidence in a Cochrane Collaboration review of data from four clinical trials in patients undergoing major abdominal or pelvic surgery; the incidence of overall VTE (DVT and PE) and symptomatic VTE was lower in the extended LMWH group (14.3% vs. 6.1%, $p < 0.0005$, and 1.7% vs. 0.2%, $p = 0.02$, respectively)[67]. Evidence about the effect of LMWH on bleeding risk after a biopsy is limited. A retrospective study in children ($n = 190$) undergoing ultrasound-guided liver biopsy showed that, for 3 major and 28 minor bleeding incidents, LMWH was a risk factor[68]. Patients scheduled to receive a biopsy can be considered low risk and be treated at the discretion of the treating physician.

Heparin-induced thrombocytopenia (HIT) is thrombocytopenia that occurs as the result of heparin use. The ACCP guidelines recommend that HIT be investigated if the individual's platelet count falls by 50% or more or if a thrombotic event occurs (or both) from day 5 to day 14 (inclusive) after initiation of heparin[59]. Strongly suspected (or confirmed) HIT, whether complicated by thrombosis or not, should be treated with an alternative non-heparin anticoagulant such as danaparoid, lepirudin, argatroban, fondaparinux (off-label), or bivalirudin[69–76]. After the platelet count has substantially recovered (usually to at least 150×10^9/L), warfarin can be started, with the non-heparin anticoagulation used as bridging therapy until the INR is therapeutic[59]. The British Committee for Standards in Haematology has issued recommendations that are concordant with those of the ACCP[66,77]. A history of confirmed or suspected HIT is a contraindication to the use of LMWH and UFH[78–80].

4. CONCLUSIONS

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. Figure 1 presents a clinical algorithm for the use of antithrombotic therapy in patients with cancer.

4.1 Summary of Recommendations on Treatment of Established VTE in Patients with Solid Tumours

Proximal lower-extremity DVT and PE are indications for antithrombotic therapy. Other VTE manifestations should be considered for antithrombotic therapy based on symptoms and risk factors. There is no consensus on duration of therapy. Trials using LMWH in cancer patients studied 3–6 months of treatment, followed by standard of care at the discretion of the treating physician. Options can include cessation of therapy, continuation of LMWH, or a switch to an oral agent. Patients with metastatic disease will continue to be at high risk for VTE and could potentially be treated indefinitely at the discretion of the treating physician[46]. Patients being treated for VTE should be aware of their condition and planned treatment; be informed of the signs and symptoms of DVT and PE, and of the side effects of anticoagulation therapy; and be instructed to inform other health care providers that they are using antithrombotic therapy. Education should be provided by health care professionals with oncology experience.

In both ambulatory patients and inpatients for whom antithrombotic therapy is not contraindicated, LMWH (that is, dalteparin, tinzaparin, or enoxaparin) is the treatment of choice because of lesser recurrence rates on treatment; however, if the patient has non-dialysis-dependent severe kidney failure, tinzaparin should be considered the agent of choice. Dalteparin is dosed subcutaneously at 200 U/kg daily for 1 month, and then 150 U/kg daily. No consensus has been reached on the dose of enoxaparin for cancer-associated thrombosis; however, for some physicians, 1 mg twice daily or 1.5 mg/kg once daily are accepted approaches[46,81,82]. Tinzaparin is dosed subcutaneously at 175 U/kg daily[47]. Unfractionated heparin can be used at the discretion of the treating physician under select circumstances only (for example, when rapid clearance of anticoagulants is desired). Typically, UFH is given intravenously at 80 U/kg, then 18 U/kg/h or according to electronic medical record algorithms or validated online dosing calculators based on partial thromboplastin time.

New oral anticoagulant agents (apixaban, dabigatran, rivaroxaban) have not yet been proved to be efficacious or safe in oncology patients. Although less favoured, oral warfarin (adjusted to INR 2–3) can be used, especially in situations in which LMWH is contraindicated or the patient refuses LMWH. Warfarin has been shown to be inferior to tinzaparin and dalteparin in randomized clinical trials in cancer patients. To

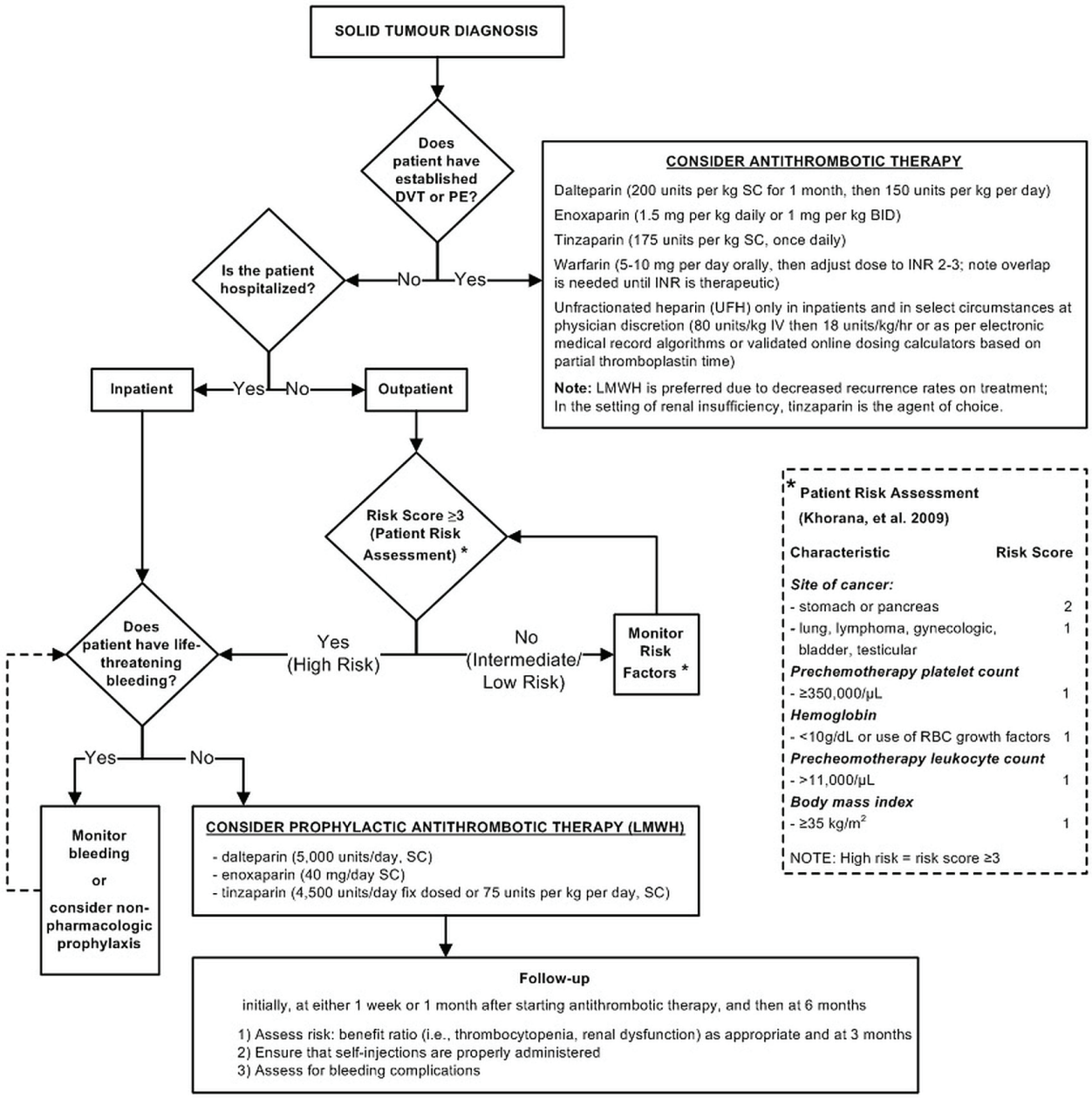

FIGURE 1 Algorithm for prophylaxis and treatment of venous thromboembolism in patients with solid tumours. DVT = deep-vein thrombosis; PE = pulmonary embolism; SC = subcutaneously; BID = twice daily; INR = international normalized ratio; IV = intravenously; LMWH = low molecular weight heparin; RBC = red blood cells.

bridge warfarin until the INR reaches the therapeutic range, LMWH or UFH should be used.

According to the ACCP guidelines[66], patients scheduled for surgery should stop LMWH 24 hours before the procedure or UFH 4–6 hours before the procedure. Therapeutic doses of LMWH and UFH should not be restarted until the high-risk period for bleeding has resolved (typically at least 3 days after surgery). In hemodynamically stable patients, LMWH or UFH for DVT prophylaxis can be initiated earlier (often on postoperative day 1).

4.2 Summary of Recommendations on VTE Prophylaxis in Patients with Solid Tumours

High-risk cancer patients (that is, patients with a Khorana risk factor score of 3 or greater[5], Table III), regardless of whether they are inpatients or outpatients, can be considered for prophylactic antithrombotic therapy at the discretion of the treating physician. The presence of a central venous catheter in the absence of other risk factors is not an indication for the use of prophylactic antithrombotic

therapy. Patients admitted to hospital should receive antithrombotic therapy for DVT prophylaxis unless contraindicated. The recommended prophylactic antithrombotic therapy is LMWH, including any of these agents: subcutaneous dalteparin (5000 U daily), subcutaneous enoxaparin (40 mg daily or 30 mg twice daily), or subcutaneous tinzaparin (4500 U daily or 75 U/kg daily). In the most recent ASCO guidelines, prophylactic anticoagulation was not globally recommended for all ambulatory oncology outpatients[48]. Patients being considered for prophylaxis with antithrombotic therapy should be informed of their risk of VTE and of the signs and symptoms of DVT and PE, as well as the side effects of anticoagulation therapy (that is, risk of bleeding). Nonpharmacologic prophylaxis (for example, compression stockings) and early mobilization should be considered for patients unable to receive pharmacologic agents (typically those who are actively bleeding).

4.3 Summary of Recommendations on Contraindications and Special Considerations with Antithrombotic Therapy

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 might require anticoagulant cessation at the discretion of the physician. Follow-up visits should assess for bleeding complications and ensure that self-injections are administered properly. Visits should occur initially between 1 week and 1 month after the start of antithrombotic therapy, and then at 6 months. A baseline complete blood count is required to ensure that anticoagulation is safe; severe thrombocytopenia might require dose adjustment or non-antithrombotic alternatives. The first follow-up complete blood count should be checked within 5–10 days of starting either LMWH or UFH to assess for HIT—a rare but life-threatening complication of heparin-based therapy. The complete blood count should then be regularly checked—at monthly intervals at a minimum.

Patients and their caretakers should be informed about VTE and its treatment. The benefits of treatment should be weighed against the risks. Patients should also be trained in self-injection with the assistance of the clinic nurse. Items that should be reviewed include VTE risk and options to lower the risk; symptoms of a blood clot, particularly PE; what to do if symptoms are suspected; the purpose of anticoagulation medication; restrictions when taking anticoagulation medication; risks of using or taking anticoagulation medication; post-thrombotic syndrome; and blood clot prevention.

5. CONFLICT OF INTEREST DISCLOSURES

MASB has no financial conflicts of interest to declare. CMJW has served on the Leo Pharma advisory board, but has no other financial conflict of interest to declare. JCE has received honoraria from Leo Pharma, Sanofi, and Pfizer.

6. REFERENCES

1. Khorana AA. Venous thromboembolism and prognosis in cancer. *Thromb Res* 2010;125:490–3.
2. Ruf W. Hemostasis and angiogenesis. In: Khorana AA, Francis CW, eds. *Cancer-Associated Thrombosis: New Findings in Translational Science, Prevention, and Treatment*. New York, NY: Informa Healthcare; 2007: 17–34.
3. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000;160:809–15.
4. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med* 2012;9:e1001275.
5. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol* 2009;27:4839–47.
6. Carrier M, Easaw J, Shivakumar S. VTE Oncology Simplified: VTE Prophylaxis in Oncology Outpatients [slide presentation]. San Francisco, CA: SlideShare at LinkedIn.com; 2013. [Available at: http://www.slideshare.net/vtesimplified/vte-prophylaxisin oncologyoutpatientsharedcareguidelineen; cited March 1, 2013]
7. Khorana AA. Risk assessment and prophylaxis for VTE in cancer patients. *J Natl Compr Canc Netw* 2011;9:789–97.
8. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111:4902–7.
9. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007;5:632–4.
10. Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. *Circulation* 2003;107(suppl 1):I17–21.
11. Prandoni P, Lensing AW, Cogo A, *et al.* The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1–7.
12. Carson JL, Kelley MA, Duff A, *et al.* The clinical course of pulmonary embolism. *N Engl J Med* 1992;326:1240–5.
13. Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000;343:1846–50.
14. Goldhaber SZ. Assessing the prognosis of acute pulmonary embolism: tricks of the trade. *Chest* 2008;133:334–6.
15. United Kingdom, National Institute for Health and Clinical Excellence (NICE). *How NICE Clinical Guidelines Are Developed: An Overview for Stakeholders, the Public and the NHS*. 4th ed. London, U.K.: NICE; 2009.
16. Cummings P, Rivara FP. Reviewing manuscripts for *Archives of Pediatrics and Adolescent Medicine*. *Arch Pediatr Adolesc Med* 2002;156:11–13.

17. AGREE Collaboration. Appraisal of Guidelines for Research and Evaluation (AGREE) instrument. Toronto, ON: AGREE Collaboration; n.d. [Downloadable from: http://www.agreetrust.org; cited November 15, 2009]
18. Mismetti P, Mille D, Laporte S, *et al.* on behalf of the CIP Study Group. Low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial. *Haematologica* 2003;88:67–73.
19. Abdelkefi A, Ben Othman T, Kammoun L, *et al.* Prevention of central venous line-related thrombosis by continuous infusion of low-dose unfractionated heparin, in patients with haemato-oncological disease. A randomized controlled trial. *Thromb Haemost* 2004;92:654–61.
20. Kakkar AK, Levine MN, Kadziola Z, *et al.* Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the Fragmin Advanced Malignancy Outcome Study (FAMOUS). *J Clin Oncol* 2004;22:1944–8.
21. Minnema MC, Breitkreutz I, Auwerda JJ, *et al.* Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. *Leukemia* 2004;18:2044–6.
22. Couban S, Goodyear M, Burnell M, *et al.* Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. *J Clin Oncol* 2005;23:4063–9.
23. Verso M, Agnelli G, Bertoglio S, *et al.* Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *J Clin Oncol* 2005;23:4057–62.
24. Karthaus M, Kretzschmar A, Kröning H, *et al.* Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Ann Oncol* 2006;17:289–96.
25. Simonneau G, Laporte S, Mismetti P, *et al.* on behalf of FX140 study investigators. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. *J Thromb Haemost* 2006;4:1693–700.
26. Riess H, Pelzer U, Hilbig A, *et al.* Rationale and design of PROSPECT-CONKO 004: a prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy. *BMC Cancer* 2008;8:361.
27. Riess H, Pelzer U, Deutschinoff G, *et al.* A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): results of the CONKO 004 trial [abstract LBA4506]. *J Clin Oncol* 2009;27:. [Available online at: http://meetinglibrary.asco.org/content/32978–65; cited April 10, 2014]
28. Young AM, Billingham LJ, Begum G, *et al.* on behalf of the WARP Collaborative Group, U.K. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP) an open-label randomised trial. *Lancet* 2009;373:567–74.
29. Agnelli G, Gussoni G, Bianchini C on behalf of the PROTECHT investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009;10:943–9.
30. Hull RD, Schellong SM, Tapson VF, *et al.* on behalf of the EXCLAIM (Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients with Prolonged Immobilization) study. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med* 2010;153:8–18.
31. Kakkar VV, Balibrea JL, Martínez–González J, Prandoni P on behalf of the CANBESURE Study Group. Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study. *J Thromb Haemost* 2010;8:1223–9.
32. Perry JR, Julian JA, Laperriere NJ, *et al.* PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost* 2010;8:1959–65.
33. Haas S, Schellong SM, Tebbe U, *et al.* Heparin based prophylaxis to prevent venous thromboembolic events and death in patients with cancer—a subgroup analysis of CERTIFY. *BMC Cancer* 2011;11:316.
34. Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann JF on behalf of the LIFENOX investigators. Low-molecular-weight heparin and mortality in acutely ill medical patients. *N Engl J Med* 2011;365:2463–72.
35. Kessler P, Pour L, Gregora E, *et al.* on behalf of the Czech Myeloma Group. Low molecular weight heparins for thromboprophylaxis during induction chemotherapy in patients with multiple myeloma. *Klin Onkol* 2011;24:281–6.
36. Palumbo A, Cavo M, Bringhen S, *et al.* Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol* 2011;29:986–93.
37. Agnelli G, George DJ, Kakkar AK, *et al.* on behalf of the SAVE-ONCO investigators. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012;366:601–9.
38. Haas SK, Freund M, Heigener D, *et al.* on behalf of the TOPIC investigators. Low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer or stage III/IV lung cancer. *Clin Appl Thromb Hemost* 2012;18:159–65.
39. Larocca A, Cavallo F, Bringhen S, *et al.* Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. *Blood* 2012;119:933–9.
40. Levine MN, Gu C, Liebman HA, *et al.* A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. *J Thromb Haemost* 2012;10:807–14.
41. Maraveyas A, Waters J, Roy R, *et al.* Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *Eur J Cancer* 2012;48:1283–92.
42. Agnelli G, Verso M, Ageno W on behalf of the MASTER investigators. The MASTER registry on venous thromboembolism: description of the study cohort. *Thromb Res* 2008;121:605–10.
43. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Venous Thromboembolic Disease.* Ver. 1.2011. Fort Washington, PA: NCCN;

2011. [Current version available online at: http://www.nccn.org/professionals/physician_gls/pdf/vte.pdf (free registration required); cited July 27, 2012]
44. Lyman GH, Khorana AA, Falanga A, *et al.* on behalf of the American Society of Clinical Oncology. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol* 2007;25:5490–505.
45. Akl EA, Vasireddi SR, Gunukula S, *et al.* Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev* 2011;:CD006649.
46. Lee AY, Levine MN, Baker RI, *et al.* on behalf of the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349:146–53.
47. Hull RD, Pineo GF, Brant RF, *et al.* on behalf of the LITE trial investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006;119:1062–72.
48. Lyman GH, Khorana AA, Kuderer NM, *et al.* Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update [Web article]. Alexandria, VA: American Society of Clinical Oncology; 2013. [Available at: http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.49.1118; cited May 13, 2013]
49. Akl EA, Terrenato I, Barba M, *et al.* Low-molecular-weight heparin vs unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. *Arch Intern Med* 2008;168:1261–9.
50. Kuderer NM, Ortel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. *J Clin Oncol* 2009;27:4902–11.
51. Institute for Clinical Systems Improvement (ICSI). Antithrombotic Therapy Supplement [Web article]. Bloomington, MN: ICSI; 2012. [Available online at: https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_cardiovascular_guidelines/antithrombotic/; cited July 26, 2012]
52. Carrier M, Khorana AA, Zwicker JI, Noble S, Lee AY on behalf of the subcommittee on Haemostasis and Malignancy for the SSC of the ISTH. Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH: a reply to a rebuttal. *J Thromb Haemost* 2014;12:116–17.
53. Verso M, Gussoni G, Agnelli G. Prevention of venous thromboembolism in patients with advanced lung cancer receiving chemotherapy: a combined analysis of the PROTECHT and TOPIC-2 studies. *J Thromb Haemost* 2010;8:1649–51.
54. Johansen KB, Balchen T. Tinzaparin and other low-molecular-weight heparins: what is the evidence for differential dependence on renal clearance? *Exp Hematol Oncol* 2013;2:21.
55. DeCarolis DD, Thorson JG, Clairmont MA, Leuthner AM, Rector TS, Johnson GJ. Enoxaparin outcomes in patients with moderate renal impairment. *Arch Intern Med* 2012;172:1713–18.
56. Cardiovascular Disease Educational and Research Trust; Cyprus Cardiovascular Disease Educational and Research Trust; European Venous Forum; International Surgical Thrombosis Forum; International Union of Angiology; Union Internationale de Phlébologie. Prevention and treatment of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). *Int Angiol* 2006;25:101–61.
57. Mahé I, Aghassarian M, Drouet L, *et al.* Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function: a comparative pharmacokinetic study. *Thromb Haemost* 2007;97:581–6.
58. Siguret V, Gouin–Thibault I, Pautas E, Leizorovicz A. No accumulation of the peak anti-factor Xa activity of tinzaparin in elderly patients with moderate-to-severe renal impairment: the IRIS substudy. *J Thromb Haemost* 2011;9:1966–72.
59. Warkentin TE, Greinacher A, Koster A, Lincoff AM on behalf of the American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133(suppl):340S–80S.
60. Siguret V, Pautas E, Février M, *et al.* Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. *Thromb Haemost* 2000;84:800–4.
61. Douketis J, Cook D, Meade M, *et al.* on behalf of the Canadian Critical Care Trials Group. Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: an assessment of safety and pharmacodynamics: the DIRECT study. *Arch Intern Med* 2008;168:1805–12.
62. Schmid P, Brodmann D, Odermatt Y, Fischer AG, Wuillemin WA. Study of bioaccumulation of dalteparin at a therapeutic dose in patients with renal insufficiency. *J Thromb Haemost* 2009;7:1629–32.
63. Schwarz RE, Marrero AM, Conlon KC, Burt M. Inferior vena cava filters in cancer patients: indications and outcome. *J Clin Oncol* 1996;14:652–7.
64. Saour J, Al Harthi A, El Sherif M, Bakhsh E, Mammo L. Inferior vena caval filters: 5 years of experience in a tertiary care center. *Ann Saudi Med* 2009;29:446–9.
65. Harvey JJ, Hopkins J, McCafferty IJ, Jones RG. Inferior vena cava filters: what radiologists need to know. *Clin Radiol* 2013;68:721–32.
66. Gould MK, Garcia DA, Wren SM, *et al.* on behalf of the American College of Chest Physicians. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(suppl):e227S–77S.
67. Rasmussen MS, Jorgensen LN, Wille–Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. *Cochrane Database Syst Rev* 2009;:CD004318.
68. Westheim BH, Østensen AB, Aagenæs I, Sanengen T, Almaas R. Evaluation of risk factors for bleeding after liver biopsy in children. *J Pediatr Gastroenterol Nutr* 2012;55:82–7.
69. Warkentin TE. Fondaparinux: does it cause HIT? Can it treat HIT? *Expert Rev Hematol* 2010;3:567–81.

70. Warkentin TE, Pai M, Sheppard JI, Schulman S, Spyropoulos AC, Eikelboom JW. Fondaparinux treatment of acute heparin-induced thrombocytopenia confirmed by the serotonin-release assay: a 30-month, 16-patient case series. *J Thromb Haemost* 2011;9:2389–96.
71. Warkentin TE. Agents for the treatment of heparin-induced thrombocytopenia. *Hematol Oncol Clin North Am* 2010;24:755–75.
72. Warkentin TE. HIT paradigms and paradoxes. *J Thromb Haemos* 2011;9(suppl 1):105–17.
73. Chong BH, Gallus AS, Cade JF, *et al.* on behalf of the Australian HIT Study Group. Prospective randomised open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopaenia with thrombosis: a clinical outcome study. *Thromb Haemost* 2001;86:1170–5.
74. Lubenow N, Eichler P, Lietz T, Greinacher A on behalf of the HIT Investigators Group. Lepirudin in patients with heparin-induced thrombocytopenia—results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost* 2005;3:2428–36.
75. Koster A, Dyke CM, Aldea G, *et al.* Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: results of the CHOOSE-ON trial. *Ann Thorac Surg* 2007;83:572–7.
76. Lewis BE, Wallis DE, Berkowitz SD, *et al.* on behalf of the ARG-911 study investigators. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation* 2001;103:1838–43.
77. Watson H, Davidson S, Keeling D on behalf of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. *Br J Haematol* 2012;159:528–40.
78. Pfizer Canada. *Fragmin: Dalteparin Sodium Injection* [product monograph]. Kirkland, QC: Pfizer Canada; 2013. [Available online at: http://www.pfizer.ca/en/our_products/products/monograph/151; cited April 12, 2013]
79. Leo Pharma. *Prinnohep: Tinzaparin Sodium. Sterile Solution for SC Injectio*n [product monograph]. Thornhill, ON: Leo Pharma; 2010. [Downloadable from: http://www.leo-pharma.ca/Home/Products/List-of-Products.aspx; cited April 12, 2013]
80. Sanofi–Aventis Canada. *Lovenox: Enoxaparin Sodium Solution for Injection* [product monograph]. Laval, QC: Sanofi–Aventis Canada; 2013. [Available online at: http://products.sanofi-aventis.ca/en/lovenox.pdf; cited April 12, 2013]
81. Merli G, Spiro TE, Olsson CG, *et al.* on behalf of the Enoxaparin Clinical Trial Group. Subcutaneous enoxaparin once or twice daily compared with IV UFH for treatment of VTE. *Ann Intern Med* 2001;134:191–202.
82. Meyer G, Marjanovic Z, Valcke J, *et al.* Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002;162:1729–35.

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