Guidance for the prevention and treatment of venous thromboembolism in cancer patients

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Venous thrombosis is a common complication in cancer patients and thromboembolism is the second most common cause of death. Several practice guidelines provide recommendations for the management of cancer-associated thrombosis. However, these guidelines do not sufficiently cover commonly encountered clinical challenges. With this expert panel, consisting of medical oncologists, haematologists, internists and thrombosis specialists, we aimed to develop a practical Belgian guidance for adequate prevention and treatment of cancer-associated thrombosis that covered several challenging situations encountered in daily clinic. This paper discusses the following topics: type and treatment duration of anticoagulant therapy, recurrent VTE despite anticoagulation, anticoagulation in case of renal impairment, liver disease and thrombocytopenia, the role of anti-Xa monitoring, central venous catheter-associated thrombosis, the position of direct oral anticoagulants and thromboprophylaxis, both in ambulatory and hospitalised patients. For an overview of the recommendations formulated by the expert panel, we refer to the key messages for clinical practice in this article.

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Introduction

It is well established that cancer patients are at increased risk of venous thromboembolism (VTE), which includes both pulmonary embolism (PE) and deep vein thrombosis (DVT). The presence of malignancy increases the risk of VTE by a factor of four.[1,2] Importantly, VTE is strongly associated with short- and long-term mortality. In fact, in cancer patients, thromboembolism represents the second most common cause of death after cancer progression.[2,3] In addition to this, VTE associated with cancer is also associated with a higher rate of recurrent thrombosis as well as bleeding.[3,4] Finally, VTE also leads to a threefold increase in hospitalisations and higher total health care costs.[5] As such, adequate prevention and treatment of cancer-associated thrombosis (CAT) is vital to reduce its burden on patients with malignancy and on the health care system as a whole.

Numerous international clinical guidelines provide recommendations to oncologists for the management of cancer-associated thrombosis.[6-10] However, some challenging clinical situations are frequently encountered by physicians caring for this patient population (e.g. thrombocytopenia, recurrent VTE, catheter-related

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thrombosis, renal impairment, etc.), which are not sufficiently addressed in these guidelines. In addition to this, there are also geographical differences in how CAT is managed. With this expert panel, consisting of medical oncologists, haematologists, internists and thrombosis specialists, we aimed to develop a practical Belgian guidance for adequate prevention and treatment of CAT and covering the challenging situations encountered in daily clinic

Methods

The purpose of this consensus paper was to provide expert guidance for challenging VTE scenarios. The specific topics to be addressed were identified by the chairmen of the working group (A. Awada and P. Verhamme). For each of the identified challenges, two experts of the panel performed an in depth literature search after which their findings were reviewed and discussed by the entire expert panel. The following eight topics were selected:

1. Type and treatment duration of anticoagulant therapy (including treatment beyond 6 months)
2. Recurrent VTE despite anticoagulation (including role of inferior vena cava [IVC] filters)
3. Anticoagulation in case of renal impairment and liver disease
4. Anticoagulation in case of thrombocytopenia
5. Anti-Xa monitoring
6. Prophylaxis of VTE in cancer patients with a Central venous catheter (CVC) and treatment of CVC-associated thrombosis
7. Direct oral anticoagulants (DOACs) and CAT
8. Prophylaxis
   a. Indication and type of prophylaxis in ambulatory patients
   b. Indication and type of prophylaxis in hospitalised patients

After discussion of these different topics reviewed and presented by two experts during a first consensus meeting (June 15th 2016), a paper was drafted. This paper was then reviewed by the members of the expert panel and finalised during a second consensus meeting (September 7th 2016). These meetings were supported by Leo Pharma at the logistical level.

Type and treatment duration of anticoagulant therapy

The standard initial treatment of an acute episode of VTE in cancer patients should consist of the administration of three to six months of subcutaneous low molecular weight heparin (LMWH) at a dose adjusted to the body weight (*Table 1*). This recommendation is based on the outcome of large randomised controlled trials.[11]

Oral anticoagulation with vitamin K antagonists (VKA) can be problematic in patients with cancer as these patients often have several co-morbidities and co-medications. Drug interactions, malnutrition and liver dysfunction can lead to wide fluctuations in the International Normalised Ratio (INR). The results of randomised clinical trials indicate that treatment with a LMWH for six months is safe and more effective than treatment with a VKA.[12,13] Studies with dalteparin implemented a dose reduction from a full-therapeutic to a subtherapeutic dose (200 to 150 anti-Xa units/kg) after four weeks, whereas studies with tinzaparin and enoxaparin were performed without dose change (175 and 150 anti-Xa units/kg, respectively) in the first three months. There are no published studies addressing optimal anticoagulation beyond six months in patients with cancer. However, it is the consensus of the panel that continuing anticoagulation beyond six months should be considered in patients with a persistent high-risk of recurrence in patients with active cancer. However, there is much debate on a firm definition of 'active disease'. In the context of this paper, the experts defined active disease as the presence of progressive tumour or ongoing cancer therapy. From six months onwards it is warranted to individualise the dosing of the LMWH to find an optimal balance between safety, the risk of recurrence and the quality of life (QoL). Of note, in patients with cancer with a first deep vein thrombosis (DVT) who were treated for 6 months with a LMWH, the absence of residual vein thrombosis identified a population at low risk for recurrent thrombotic events.[14]

A special case was made for patients that are treated in a curative setting (adjuvant therapy). This includes breast cancer patients receiving tamoxifen or chemotherapy in the adjuvant setting. In line with the ESMO guidelines, it was concluded that these patients should be treated with a LMWH for six months, though oral treatment was considered to be an alternative option for selected patients.[9]

Recurrent VTE despite anticoagulation

The rate of recurrent VTE despite anticoagulation remains high in cancer patients and is associated with a poor prognosis. A systematic review of 1,292 patients with cancer showed that VTE recurrence rates with

LMWH and VKA were 6.5% and 17.9% respectively.[15] The risk of recurrence is highest during the 1st month of anticoagulation.

Patients with recurrent VTE, despite standard doses of anticoagulant therapy, should be assessed for treatment compliance, heparin-induced thrombocytopenia (HIT), or any evidence of mechanical compression resulting from malignancy. If a patient is treated with VKA, it is recommended to switch to a LMWH. However, the reverse does not hold true: switching from a LMWH to VKA in case of VTE recurrence should not be considered. If a patient is treated with a sub-therapeutic LMWH dose, it is recommended to return to the therapeutic dose. If a therapeutic dose is already given, the dose can be escalated by 20% to 25%.[16] In case of supra-therapeutic dosing, twice daily dosing of the LMWH was recommended by the expert panel. If moving to supra-therapeutic levels, anti-Xa monitoring should be considered when feasible. In some cases, the addition of low-dose aspirin can be considered, although firm evidence for this is lacking.

The expert group advises against the routine use of an IVC filters in patients who present with recurrent VTE despite therapeutic anticoagulation. This should only be considered in selected cases.

Table 1. LMWH doses for the treatment of acute VTE in Belgium.

LMWH	Recommended dose
Once Daily	
Tinzaparin (Innohep®)	175 U/kg/24h
Dalteparin (Fragmin®)	200 U/kg/24h
Nadroparin (Fraxodi®)	0.1 ml/10kg/24h
Enoxaparin (Clexane®)	1.5 mg/kg/24h
Twice Daily	
Dalteparin (Fragmin®)	100 U/kg/12h
Nadroparin (Fraxiparine®)	0.1 ml/10kg/12h
Enoxaparin (Clexane®)	1 mg/kg/12h

Anticoagulation in case of renal impairment

Renal impairment is a common problem in cancer and is associated with a higher bleeding risk. The safe use of LMWHs implies a preserved renal function (GFR >50 ml/min). In patients with lower GFR (30-50 ml/min), LMWHs remain the first choice but bioaccumulation can already occur. The most important risk of bleeding concerns patients with severe renal impairment (GFR <30 ml/min). LMWHs with little bioaccumulation (e.g. dalteparin, tinzaparin) are preferred in patients with severe renal impairment.[17]

Dose adjustment based on anti-Xa monitoring was suggested in patients with CrCl <30 ml/min, however evidence for a clear benefit of this approach is lacking. For severely renally impaired patients with acute VTE, intravenous unfractionated heparin with aPTT monitoring is recommended for the initial treatment. In fact, patients with solid tumours and such a low creatinine clearance are usually in a very bad shape and are better managed in the hospital.

For a more complete overview on the management of cancer-associated thrombosis (CAT) in renally impaired patients we also refer to the letter to the editor of professor Hougardy and professor Motte in the same issue of this journal.

Anticoagulation in case of liver disease

The data on the treatment of CAT in patients with liver disease are limited. In a preventive study, it was shown that twelve months of enoxaparin was safe and effective in preventing portal vein thrombosis in patients with cirrhosis and a Child-Pugh score of 7-10.[18] This effect was associated with improved survival.

LMWHs are believed to be safe in patients with comorbid liver disease. However, the clinician needs to assess the indication of LMWH case by case in patients with liver disease. Of note, the anti-Xa assay is difficult in patients with liver disease and might underestimate the true degree of anticoagulation, which could lead to incorrect dose adaptation and subsequent morbidity and mortality.

Anticoagulation in case of thrombocytopenia

There are no trial data on the anticoagulation of cancer patients with thrombocytopenia. Before moving to treatment, one must first search for the aetiology of the thrombocytopenia (treatment-related, bone marrow

involvement of the cancer, idiopathic thrombocytopenic purpura [ITP], or heparin-induced thrombocytopenia [HIT]). In this light one must exclude a reversible, or treatable cause. For the treatment of CAT with thrombocytopenia, the expert group endorses the recommendation of the International Society on Thrombosis and Haemostasis (ISTH) on this matter.[19] Full therapeutic doses of anticoagulation with LMWHs are recommended without platelet transfusion in patients with CAT and a platelet count of 50 x109/L or higher and no clinical signs of bleeding. In case of acute CAT and thrombocytopenia (platelet count below 50 x109/L) full therapeutic doses of anticoagulation are recommended; in these patients platelet transfusion to maintain a platelet level of 50 x109/L or higher should be considered. For subacute or chronic CAT and thrombocytopenia (platelet count below 50 x109/L) it is recommended to reduce the LMWH dose to 50% of the therapeutic dose or to use a prophylactic dose of LMWH in patients with a platelet count between 25 and 50 x109/L. In patients with a platelet count below 25 x109 discontinuing anticoagulation is suggested.

For thrombopenic patients who need LMWH prophylaxis, consider case-by-case approach between 20 and 50 x109/L. Below 20 x109/L platelets, no prophylaxis is recommended (except for some hematologic patients).

Anti-Xa monitoring

LMWHs have predictable pharmacodynamic profiles and wide therapeutic windows that do not require routine coagulation monitoring in clinically stable and uncomplicated patients. Anti-Xa is a surrogate marker that measures the anticoagulant effect of LMWH and is assumed to correlate with haemorrhagic and thromboembolic events.

From a practical point of view, there are large variations between reagents used in anti-Xa assays and between laboratories, limiting their utility. Moreover, target anti-Xa levels are not clinically validated and there are no standardised methods to adjust LMWH doses based on anti-Xa levels. In fact, there are no data suggesting that adjusting the LMWH dose based on peak anti-Xa levels is correlated with improved safety and efficacy.

Peak anti-Xa levels (blood sampling four hours after injection) should not be utilised to evaluate prophylactic or therapeutic LMWH dosing regimens in routine clinical practice. In selected patient populations (e.g. severe renal impairment), trough anti-Xa levels (blood sampling before the next injection) may have a role in evaluating LMWH accumulation and the need to adjust the dose or prolong the dosing interval (trough target <0.4 IU/mL).

Only limited data are available on the use of anti-Xa levels to monitor and adjust LMWH daily doses in patients with severe renal impairment (<30 ml/min).[20] Anti-Xa levels remain of limited value in patients with renal impairment because they are poorly correlated with bleeding, especially in patients with high risk of bleeding complications.[21]

Prophylaxis of VTE in cancer patients with a CVC and treatment of CVC-associated thrombosis

Central venous catheters (CVC) are associated with upper extremity DVT and PE and are independent risk factors for VTE. Recent studies and a meta-analysis of randomised controlled trials on this matter did not show clinically meaningful degrees of protection against catheter-induced VTE using either low-dose warfarin or LMWH in patients with cancer.[22,23,19] As such, the expert group does not recommend primary prophylaxis for cancer patients with a CVC, unless in patients with a very high VTE risk (e.g. patients with a femoral catheter).

A diagnosis of a CVC-related thrombosis should be confirmed by ultrasonography. If there is a high suspicion for a CVC-related thrombosis despite a negative ultrasonography, a venography, or CT venography is preferred over a repeated ultrasonography.

For the treatment of CVC-related VTE, LMWH is the preferred treatment. Local thrombolysis is not routinely recommended, but may be occasionally considered. The catheter should be left in place if the symptoms improve upon anticoagulation and if the catheter is still needed, functions properly and is not infected. Patients with CVC-associated thrombosis should be treated for 3 months. When the catheter remains in place and is still used for chemotherapy and the bleeding risk is low, the panel recommends prolonging the thromboprophylaxis for as long as the chemotherapy is given, and/or in cases where venous access is precious. If the catheter is removed one should not treat longer than three months. A shorter period can be considered if there is complete resolution of the thrombus.

LMWH is the preferred treatment for long-term prevention, but the dose can be adjusted based on the assessment of the bleeding risk. Oral treatment can be considered if subcutaneous administration is poorly tolerated.[23]

Direct oral anticoagulants (DOACs) and CAT

None of the recently introduced direct oral anticoagulants (DOAC) (rivaroxaban, dabigatran, apixaban and edoxaban) was specifically tested in cancer patients, and in all of the studies with these agents the control arm received VKA instead of LMWH (the current standard of care). Therefore, the safety and efficacy of DOACs in patients with CAT remains uncertain. As such, the expert panel concluded that LMWH should remain the preferred treatment option for both the initial and long-term treatment of CAT, awaiting the result of ongoing studies.

Nevertheless, in some cases DOACs could form an alternative for non-progressive cancer patients (e.g. breast cancer patients with thrombosis while under adjuvant therapy with tamoxifen). DOACs could also be an alternative for patients who can no longer tolerate parenteral therapy. In these cases, the ease of use of DOACs may be preferred over the disadvantages of VKA (e.g. small window of efficacy). However, when opting for a DOAC one should take into account the specific metabolic pathways and the route of elimination of these agents (to avoid drug-drug interactions) and ask for advice from a haemostasis specialist.

Prophylaxis

Indication and type of prophylaxis in ambulatory patients

The incidence of VTE is highly heterogeneous in the cancer population ranging from 0.6 to 26 %.[24] The Khorana score is the only validated score to assess the risk of VTE, but with limitations of not being representative of all tumour categories and not prospectively tested in clinical trials.[25] Several studies have assessed thromboprophylaxis of ambulatory cancer patients under chemotherapy.[26-28] Despite the fact that these studies consistently demonstrate a benefit for thromboprophylaxis, the difference in absolute risk was very small (to avoid 1 event, 46-60 patients should be treated). Combined with the important cost (and risk) of LMWHs, these findings did not convince the expert group to recommend routine thromboprophylaxis in ambulatory cancer patients.

A special exception is made for patients with multiple myeloma receiving thalidomide- or lenalidomide-based therapy. The risk for VTE in these patients is very high and ranges from 12% to 28%. Two randomised trials have been published comparing VTE prophylaxis and observation.[29,30] In these studies, both aspirin and LMWH were shown to be acceptable thromboprophylaxis options (with slightly greater efficacy of LMWH). Based on these findings, the expert panel recommends thromboprophylaxis with aspirin for low-risk multiple myeloma patients and with LMWH for patients with a high thrombosis risk.

In addition to this, the expert panel indicated that thromboprophylaxis with LMWH could be considered for selected patients at particularly high risk, such as pancreatic cancer patients receiving chemotherapy with a low risk of bleeding.

Indication and type of prophylaxis in hospitalised patients

Three large randomised phase III studies reported a significant reduction in VTE following prophylactic treatment with LMWH, or fondaparinux in medically ill hospitalised patients.[31-33] However, no specific studies on the use of thromboprophylaxis in hospitalised, non-surgical cancer patients have been conducted. A recent meta-analysis of the cancer population in three placebo-controlled trials on thromboprophylaxis failed to show a significant reduction in the incidence of VTE when pharmacological anticoagulation was used.[34] The expert panel supports the use of thromboprophylaxis with LMWHs in all cancer patients with progressive disease hospitalised for an acute medical complication and who are bedridden. For all other cases (e.g. paucisymptomatic disease), other risk factors should be taken into account (e.g. restricted mobility, obesity, history of VTE, stage and histology of the cancer, race, platelet count, presence of CVC, use of anti-angiogenic agents, etc.)

For cancer patients who are hospitalised in a surgical setting, the situation is easier. In patients with malignant disease undergoing a major surgical intervention, thromboprophylaxis with LMWH for at least 7-10 days is recommended. In patients with high-risk features, the prophylaxis can be extended up to four weeks.

Of note, mechanical methods of thromboprophylaxis (graduated compression stockings [GCS], intermittent pneumatic compression [IPC]) can be used in high-risk surgical patients with a contra-indication for pharmacological thromboprophylaxis. In this respect, IPC should be preferred over GCS when available.

References

1. Horsted F, West J, Grainge M, et al. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analyis. PLoS Med 2012;9:e1001275.

2. Khorana A, Francis C, Culakova E, et al. Frequency, risk factors and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007;110:2339-46.

3. Khorana A, Francis C, Culakova E, et al. Thromboembolism is a leading cause

Key messages for clinical practice

1. Type and treatment duration of anticoagulant therapy
   - 3 to 6 months of LMWH is the preferred initial treatment for CAT.
   - In case of active disease, or when risk of recurrence remains high, treatment can be prolonged beyond 6 months.

2. Recurrent VTE despite anticoagulation
   - Assess for treatment compliance, HIT or any evidence of mechanical compression resulting from malignancy.
   - If treated with VKA, switch to LMWH.
   - If LMWH dosing is sub-therapeutic, move towards therapeutic dose.
   - If therapeutic dosing, increase dose with 20%-25%. Twice daily dosing is preferred.
   - IVC filters to be considered in very selected patients.

3. Anticoagulation in case of renal impairment and liver disease
   - Caution is warranted in the anticoagulation of cancer patients with renal impairment given the increased bleeding risk resulting from bio-accumulation.
   - In patients with a severe renal impairment, the use LMWHs that are less depending on clearance by the kidney (i.e. dalteparin, tinzaparin) is preferred.
   - LMWHs appear to be safe in patients with comorbid liver disease. In cases with severe liver disease the clinician needs to assess the indication of LMWH on a case-by-case basis.

4. Anticoagulation in case of thrombocytopenia
   - Platelet count of 50 x109/L or higher and no clinical sign of bleeding: full dose LMWH without platelet transfusion.
   - Platelet count below 50 x109/L and acute CAT: full dose LMWH and consider platelet transfusion to maintain a platelet level of 50 x109/L or higher.
   - Platelet count between 25 and 50 x109/L and subacute or chronic CAT: reduce LMWH dose by 50%, or use a prophylactic dose of LMWH.
   - Platelet count below 25 x109: discontinue anticoagulation.

5. Anti-Xa monitoring
   - Routine anti-Xa monitoring is not needed, only to be considered in special cases (recurrence during optimal anticoagulation, renal impairment).
   - If anti-Xa monitoring is used to exclude accumulation, measurement of trough levels is recommended.

6. Prophylaxis of VTE in cancer patients with a CVC and treatment of CVC-associated thrombosis
   - Primary prophylaxis for cancer patients with a CVC is not recommended.
   - Diagnosis of a CVC-related thrombosis should be confirmed by ultrasonography.
   - LMWH for at least 3 months is the preferred treatment option. Extend therapy for as long as catheter is in place can be considered.
   - Catheter can be left in place if the symptoms improve upon anticoagulation and if the catheter is still needed, functions properly and is not infected.

7. Direct oral anticoagulants (DOACs) and CAT
   - LMWHs remain the preferred treatment option for both the initial and long-term treatment of CAT.
   - The safety and efficacy of DOACs in patients with CAT remains uncertain. Results of clinical trials are awaited.

8. Prophylaxis
   - Indication and type of prophylaxis in <u>ambulatory</u> patients.
     - Routine thromboprophylaxis in ambulatory cancer patients is not recommended.
     - Thromboprophylaxis can be considered in selected patients:
       - Multiple myeloma patients treated with immunomodulatory agents, or carfilzomib.
       - Pancreatic cancer patients receiving chemotherapy with a low risk of bleeding.
   - Indication and type of prophylaxis in <u>hospitalised</u> patients.
     - In patients with malignant disease undergoing a major surgical intervention, thromboprophylaxis with LMWH for at least 7-10 days is recommended.
     - It is recommended to extend prophylaxis to 4 weeks in high-risk situations.
     - Thromboprophylaxis with LMWHs can be considered in all active cancer patients hospitalised for a medical illness.
     - For all other cases, specific risk factors for VTE should be taken into account.

of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5(3):632-4.

4. Prandoni P, Lensing A, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100(10):3484-8.

5. Khorana A, Dalal M, Lin J, et al. Health care costs associated with venous thromboembolism in selected high-risk ambulatory patients with solid tumours undergoing chemotherapy in the United States. Clinicecon Outcomes Res 2013;5:101-8.

6. Kearon C, Akl E, Ornelas J, et al. Antithrombotic therapy for VTE disease. Chest 2016;149(2):315-52.

7. Lyman G, Bohlke K, Khorana A, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical oncology clinical practice guideline update 2014. J Clin Oncol 2015;33(6):654-6.

8. Streiff MB, Holmstrom B, Ashrani A, et al. Cancer-Associated Venous Thromboembolic Disease, Version 1.2015. J Natl Compr Canc Netw 2015;13(9):1079-95.

9. Mandalà M, Falanga A, Roila F, et al. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22 Suppl 6:vi85-92.

10. Khorana A, Carrier M, Garcia D, et al. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. J Thromb Thrombolysis 2016;41(1):81-91.

11. Akl E, Labedi N, Barba M, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane database Syst Rev 2011;6:CD006650.

12. Lee A, Levine M, Baker R, 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;349:146-153.

13. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular weight heparin and warfarin for the secondary prevention or recurrent venous thromboembolism in patients with cancer: a randomized controlled trial. Arch Intern Med 2002;162:1729-35.

14. Romera-Villegas A, Cairols-Castellote M, Vila-Coll R, et al. Long-term use of different doses of low-molecular-weight heparin versus vitamin K antagonists in the treatment of venous thromboembolism. Ann Vasc Surg 2010;24:628-39.

15. Carrier M, Le Gal G, Cho R, et al. Dose escalation of low-molecular-weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Haemost 2009;7:760-5.

16. Di Nisio M, Carrier M, Lyman G, et al. Prevention of venous thromboembolism in hospitalized medical cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost 2014;12(10):1746-9.

17. Easaw J, Shea-Budgell M, Wu C, et al. Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment. Curr Oncol 2015;22(2):144-55.

18. Villa E, Cammà C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143(5):1253-60.e1-4.

19. Carrier M, Kohrana A, Zwicker J, et al. Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH. J Thromb Haemost 2013;11(9):1760-5.

20. Nutescu E, Spinler S, Wittkowsky A, et al. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009;43(6):1064-83.

21. Brophy D, Martin E, Gehr T, et al. Enhanced anticoagulant activity of enoxaparin in patients with ESRD as measured by thrombin generation time. Am J Kidney Dis 2004;44(2):270-7.

22. Brophy D, Martin E, Gehr T, et al. Thrombin generation time is a novel parameter for monitoring enoxaparin therapy in patients with end-stage renal disease. J Thromb Haemost 2006;4(2):372-6.

23. Debourdeau P, Farge D, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. J Thromb Haemost 2013;11(1):71-80.

24. Carrier M, Lazo-Langner A, Shivakumar S, et al. Clinical challenges in patients with cancer-associated thrombosis: Canadian expert consensus recommendations. Curr Oncol 2015;22(1):49-59.

25. Khorana A, Connoly G, et al. Assessing risk of venous thromboembolism in patient with cancer. J Clin Oncol 2009;27(29):4839-47.

26. Khorana A, Kuderer N, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111(10):4902-7.

27. Akl E, Gunukula S, Barba M, et al. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane Database Syst Rev 2011;(4):CD006652.

28. Di Nisio M, Porreca E, Ferrante N, et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev 2012;(2):CD008500.

29. Akl E, Schünemann H. Routine heparin for patients with cancer? One answer, more questions. N Engl J Med 2012;366(7):661-2.

30. 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(8):986-93.

31. 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(4):933-9.

32. Cohen A, Davidson B, Gallus A, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332(7537):325-9.

33. Samama M, Cohen A, Darmon J, et al. comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341(11):793-800.

34. Leizorovic A, Cohen A, Turpie A, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005;165(3):341-5.

35. Carrier M , Khorana A, Moretto P, et al. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. Am J Med 2014;127(1):82-6.e1.

36. Napolitano M, Saccullo G, Malato A, et al. Optimal duration lof low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: The Cancer-DACUS study. J Clin Oncol 2014;32(32):3607-12.