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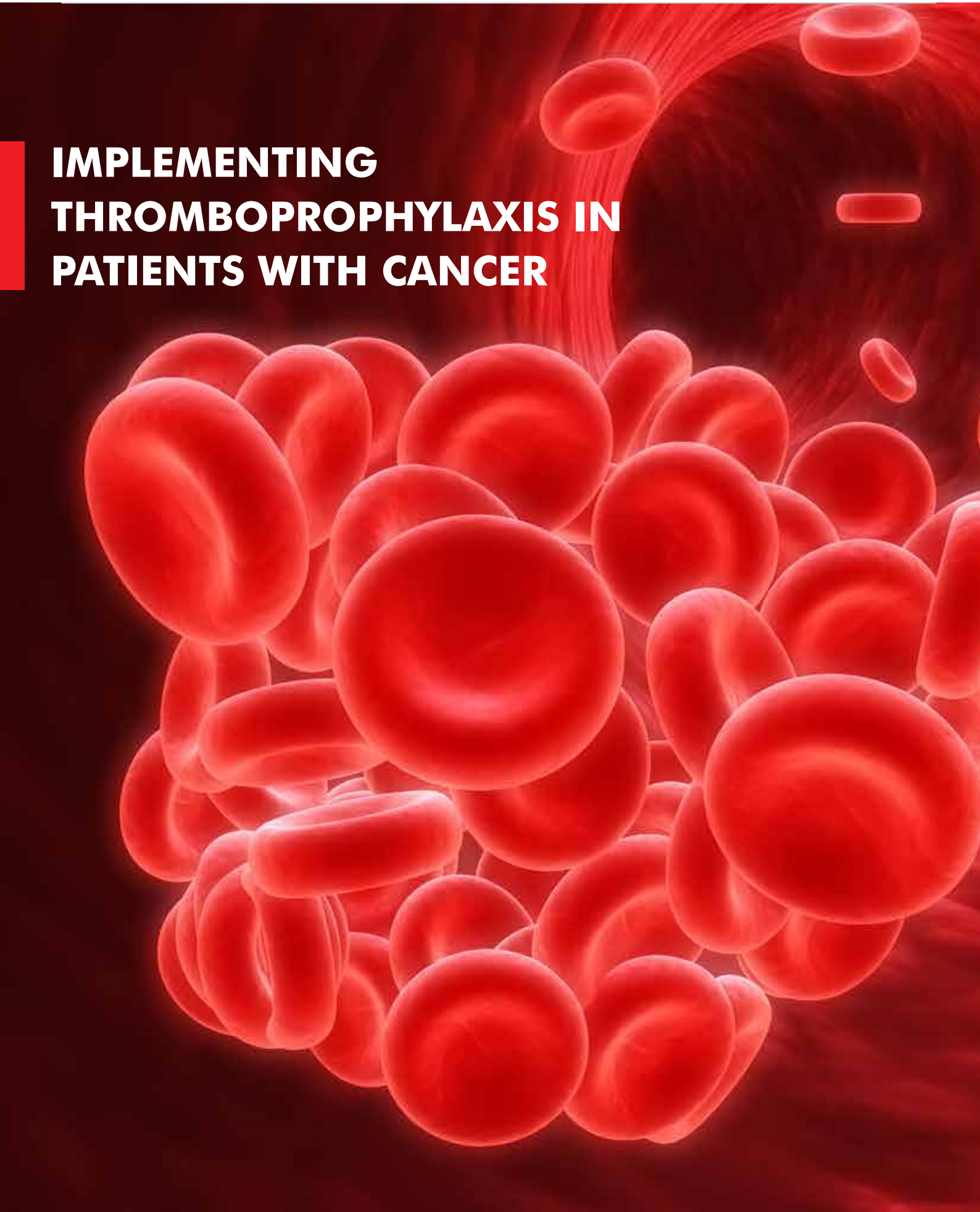
IMPLEMENTING THROMBOPROPHYLAXIS IN PATIENTS WITH CANCER



Learning Objectives

At the end of this educational content, the reader will gain a fair idea about:

1. Importance of thromboprophylaxis in patients with cancer in different clinical settings
2. Recommended guidelines of VTE management in patients with cancer, in different clinical scenarios

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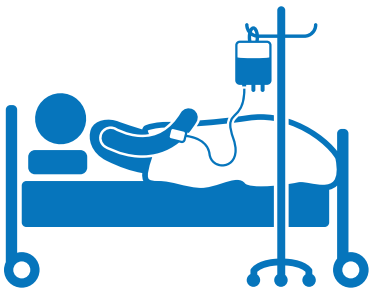
Thromboprophylaxis in Patients with Active Cancer – Hospitalized, Undergoing Surgery, Chemotherapy, Outpatient/Ambulatory

A systemic review and meta-analysis of 33 trials with 11,942 cancer patients showed that:

In patients with cancer undergoing surgery: Administration of thromboprophylaxis is associated with **decrease in venous thromboembolism** (VTE; relative risk [RR]: 0.51, 95% confidence interval [CI]: 0.32–0.81) [Figure 1] and deep vein thrombosis (DVT; RR: 0.53, 95% CI: 0.33–0.87).[1]

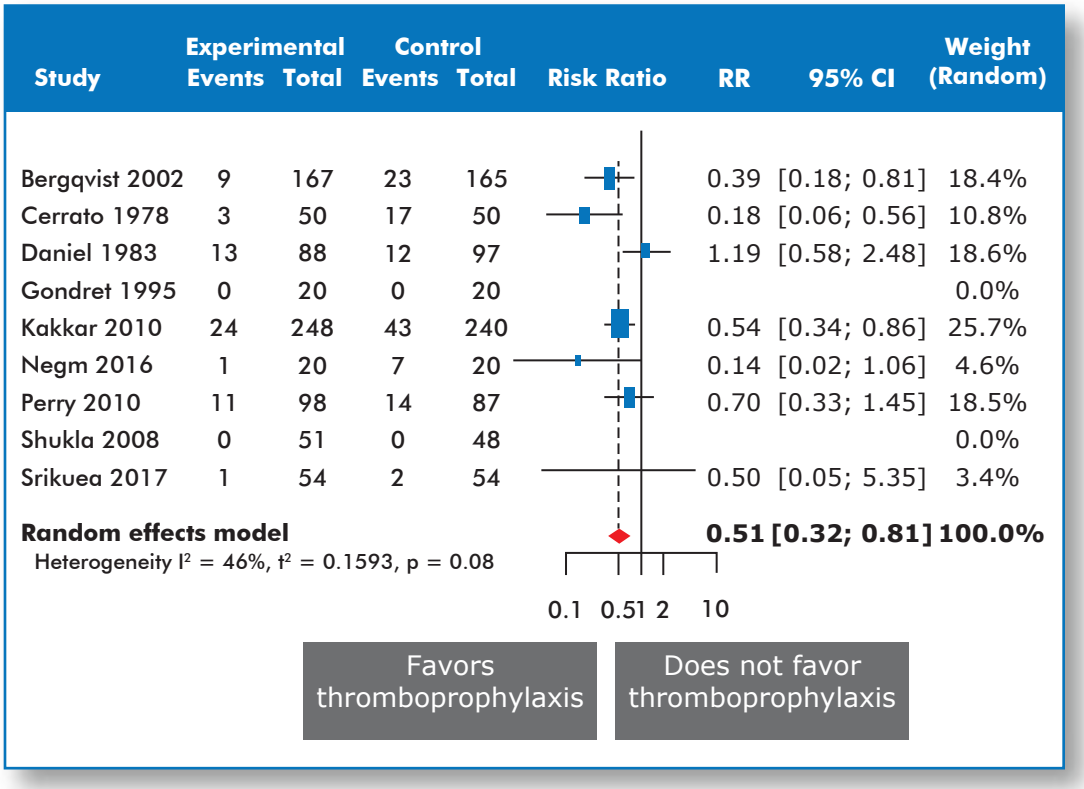


In patients with cancer undergoing chemotherapy: Administration of thromboprophylaxis reduces the incidences of VTE, DVT, and pulmonary embolism (PE) compared with no thromboprophylaxis (RR: 0.54, 95% CI: 0.40–0.73; RR: 0.47, 95% CI: 0.31–0.73; RR: 0.51, 95% CI: 0.32–0.81, respectively).[1]

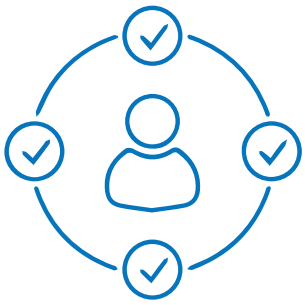
Thromboprophylaxis is needed, as **VTE is a serious complication in patients with active cancer undergoing surgery and chemotherapy.** Moreover, the **prevalence of VTE is increasing every year.** Extensive tissue and vascular injury, postoperative tissue factor exposure, procoagulant active cytokine release, and postoperative patient activity can lead to VTE.

Additionally, chemotherapy causes vascular endothelial injury, initiates endothelial procoagulant mechanisms, reduces the levels of anticoagulants, and increases the levels of type I plasminogen

Figure 1: Forest plot of VTE in cancer patients undergoing surgery



activator inhibitors. **Thromboprophylaxis has been shown to reduce VTE events without increasing the incidence of major bleeding in patients with cancer undergoing surgery or chemotherapy.**[1]



Four large studies (PROTECHT, Myeloma study, PROSPECT-CONKO-004, and FRAGEM trial) on VTE prophylaxis of cancer patients in the outpatient setting have been conducted. In PROTECHT trial, overall low event rate in the study did not lead to recommendations for prophylaxis or to widespread clinical adoption. In a study in myeloma patients, no significant differences between thromboprophylaxis groups in terms of VTE incidence and bleeding events were noticed.

PROSPECT CONKO-004 trial showed that thromboprophylaxis can **safely and significantly reduce rates of VTE in the outpatient population**. FRAGEM trial provided support for considering thromboprophylaxis in this clinical setting.[2]

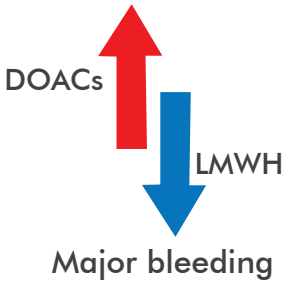
Factors to Consider while Implementing Thromboprophylaxis in Patients with Cancer

Efficacy and safety of anticoagulants

LMWH

Due to the superior efficacy of low molecular weight heparin (LMWH), as compared to vitamin K antagonists (VKAs) in several randomized controlled trials, **LMWH is recommended for treatment and secondary prevention of VTE in patients with active cancer.**[3]

Risk of bleeding

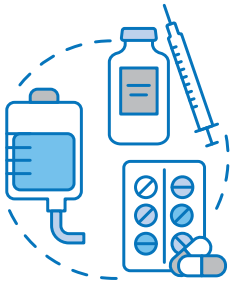


Clinicians should determine the risk–benefit ratio when tailoring the anticoagulation therapy of patients with active cancer and estimate the risks of major bleeding complications. They should also consider tumor types (for example, urothelial cancer) and features associated with high risk for bleeding, including gastrointestinal mucosal abnormalities (for example, mucositis); recent bleeding or prior major bleeding; thrombocytopenia; renal impairment; and antiplatelet use. **A higher risk of major bleeding complications has been seen in patients using direct oral anticoagulants (DOACs) as compared to those using LMWH in HOKUSAI and SELECT-D trials.**[3]

Patient preference

Consideration of patient preference, drug cost, and coverage during therapy selection may improve adherence.[3]

Drug interactions



Evaluating potential drug–drug interactions is important when selecting the appropriate thromboprophyaxis agent with anticoagulant therapy. This evaluation may include considering the potential for any direct toxicity that might occur with the concomitant use of anticoagulant regimens and acetylsalicylic acid or nonsteroidal anti-inflammatory drugs and any potential pharmacokinetic interactions.[3]

Renal impairment

LMWH might be preferable over DOACs in patients with CAT and a creatinine clearance of 30–50 mL/min, especially if additional risk factors for bleeding are present.[3]

Gastrointestinal surgery or absorption disorders

DOACs are absorbed through the gastrointestinal tract. So, in **patients with gastrointestinal surgery and absorption disorders**, there may be **significant reduction in absorption of DOACs**.[3]

Pre-existing conditions and co-medication

The patient's pre-existing conditions and concurrent medications with respect to the efficacy and safety of any anticoagulant should also be taken into consideration.[3]

Optimal Selection of Anticoagulants

Anticoagulants[4]	Optimal preference[4]	Avoid[4]
LMWH	• Frequent emetogenic chemotherapy, difficulty with oral intake • Concerns for gastrointestinal absorption (feeding tubes, gastric/bowel resections) • Drug-drug interactions with DOAC or VKA • Known increased bleeding risk • Recurrent cancer-associated VTE while on anticoagulants	• Strong aversion to injectable therapy • Renal insufficiency/ fluctuating renal status# • Extremes of weight (<50 kg or >150 kg)
DOAC (may differ for individual agents)	• Patient without gastrointestinal malignancy • Low risk of major bleeding • Ease of treatment for a patient is a priority • No strong drug-drug interactions	• Active gastrointestinal/ malignancy • History of gastrointestinal bleeding • Extremes of weight (<50 kg or >150 kg) • Renal insufficiency/ fluctuating renal status

Anticoagulants[4]	Optimal preference[4]	Avoid[4]
VKA	• Any situation in which close anticoagulant monitoring is necessary (multiple prior bleeds) or concern about absorption and metabolism • Advanced chronic kidney disease • Extremes of weight (<50 kg or >150 kg)	• Lack of access to dedicated anticoagulation monitoring service with experience caring for patients with cancer

DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism; LMWH, low molecular weight heparin

#If LMWH is used in patients with severe renal insufficiency (CrCl <30 mL/min) who require therapeutic anticoagulation, 50% of the dose is recommended.[5]

Guideline Recommendations

Recommendations in hospitalized/medical cancer patients

Thromboprophylaxis is recommended in hospitalized/medical cancer patients.[6,7,8]

ASCO (2019)[6]	ITAC (2019)[7]	ESMO[8]
• In active malignancy and acute medical illness/reduced mobility/without additional risk factors, offer pharmacologic thrombo-prophylaxis in the absence of bleeding/other contraindications • No routine pharmacologic thrombo-prophylaxis in patients admitted for minor procedures/ chemotherapy infusion/stem-cell transplantation/ bone marrow transplantation	• Prophylaxis with LMWH or fondaparinux when CrCl is ≥30 mL/min, or with UFH in hospitalized patients with cancer and reduced mobility • DOACs not recommended routinely	Prophylaxis with UFH, LMWH, or fondaparinux in hospitalized cancer patients confined to bed with an acute medical complication

ASCO, American Society of Clinical Oncology; ITAC, International Initiative on Thrombosis and Cancer; ESMO, European Society for Medical Oncology; CrCL, creatinine clearance; UFH, unfractionated heparin; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant.

Recommendations in cancer patients undergoing surgery

Thromboprophylaxis is recommended in cancer patients undergoing surgery.[6,7,8]

ASCO (2019)[6]	ITAC (2019)[7]	ESMO[8]
• Preoperative pharmacologic thrombo-prophylaxis with UFH/LMWH unless contraindicated • Pharmacologic thrombo-prophylaxis should be continued for 7 to 10 days • Extended prophylaxis with LMWH up to 4 weeks postoperatively after major open/laparoscopic abdominal/pelvic surgery for high-risk cancer (restricted mobility, obesity, VTE history) • Pharmacologic + mechanical prophylaxis in the highest-risk patients	• Use LMWH once daily (CrCL ≥30 mL/min) or low-dose UFH thrice daily • Start pharmacologic prophylaxis 2–12 h preoperatively and continue for 7–10 days • Use the highest prophylactic dose of LMWH in patients with cancer • Extended LMWH prophylaxis (up to 4 weeks) after major laparotomy/ laparoscopic surgery in patients with cancer with high VTE and low bleeding risk	• Prophylaxis with LMWH/UFH recommended • Patients with cancer undergoing elective major abdominal or pelvic surgery should receive in hospital and post-discharge prophylaxis with LMWH for up to 1 month after surgery

ASCO, American Society of Clinical Oncology; ITAC, International Initiative on Thrombosis and Cancer; ESMO, European Society for Medical Oncology; CrCL, creatinine clearance; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

Recommendations in outpatients/ambulatory patients with cancer on chemotherapy

Thromboprophylaxis is recommended in outpatients/ambulatory patients with cancer on chemotherapy.[6,7]

ASCO (2019)[6]	ITAC (2019)[7]
• High-risk outpatients with cancer: Prophylaxis with LMWH/apixaban/rivaroxaban in case no bleeding and drug interactions • Patients with multiple myeloma and on chemotherapy and/or dexamethasone: Prophylaxis with aspirin/LMWH for lower-risk patients and LMWH for higher-risk patients.	• Prophylaxis with LMWH recommended in ambulatory patients with locally advanced/metastatic pancreatic cancer on chemotherapy with low bleeding risk • Prophylaxis with DOAC recommended in patients at intermediate-to-high risk of VTE, identified by cancer type or by a Khorana score ≥2 with no high risk of bleeding • VTE prophylaxis in patients treated with immunomodulatory drugs + steroids/systemic anticancer therapies: VKAs (low/therapeutic doses), LMWH (prophylactic doses), and low-dose aspirin.

ASCO, American Society of Clinical Oncology; ITAC, International Initiative on Thrombosis and Cancer; ESMO, European Society for Medical Oncology; VKA, vitamin K antagonist; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant.

Case Study - 01

A 62-year-old male patient with metastatic gastric carcinoma receiving palliative chemotherapy was admitted to the emergency ward with a 3-day history of acute pain, swelling, and erythema of the right lower limb. He had a past medical history of gastrointestinal bleeding and was diagnosed with proximal lower limb DVT.

What would be the anticoagulant regimen for treatment of VTE in this patient?

A. UFH

B. DOACs

C. LMWH

D. VKAs

Answer: **C**

Explanation: LMWH is the choice of anticoagulant in cancer patients with a high risk of bleeding, those with gastrointestinal or urothelial cancer, or those taking concomitant medications that may lead to serious drug–drug interactions with DOACs. According to the ASCO 2019 guidelines, the LMWH regimen for VTE treatment of cancer patients in this setting is 1.5 mg/kg once daily and 1 mg/kg every 12 hours.

Case Study - 02

A 70-year-old obese woman with active cancer was admitted for open abdominal surgery. The patient was initially started on a prophylactic dose of LMWH. A close follow-up appointment was scheduled to ensure no bleeding complications.

How long should anticoagulant therapy be continued after surgery?

A. For lifetime
B. Till the patient gets discharged
C. Not needed after surgery
D. 4 weeks postoperatively

Answer: **D**

Explanation: The ASCO 2019 guideline recommends extended LMWH up to 4 weeks postoperatively after major open/ laparoscopic abdominal/pelvic surgery for high-risk cancer (restricted mobility, obesity, VTE history).

Take Home Points

- VTE is the second most common cause of death in hospitalized cancer patients after cancer itself.[9]
- Thromboprophylaxis is recommended in hospitalized/medical cancer patients, in cancer patients undergoing surgery, and in outpatient/ambulatory cancer patients on chemotherapy.[6,7,8]
- Several guidelines recommend extended thromboprophylaxis with LMWH for 4 weeks postoperatively after major open/laparoscopic abdominal/pelvic surgery for high-risk cancer.[6,7,8]

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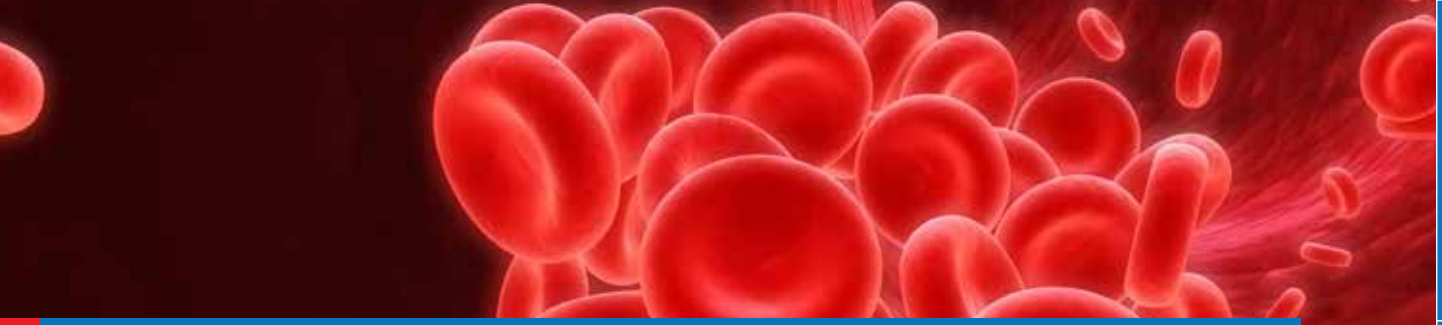

References

1. Liu M, Wang G, Li Y, *et al*. Efficacy and safety of thromboprophylaxis in cancer patients: A systemic review and meta-analysis. *Ther Adv Med Oncol*. 2020 Mar 18;12:1758835920907540.

2. Menapace LA, Khorana AA. The role of thromboprophylaxis in cancer patients: Emerging data. *Curr Opin Hematol*. 2010 Sept;17(5):450–6.

3. Carrier M, Blais N, Crowther M, *et al*. Treatment algorithm in cancer-associated thrombosis: Canadian expert consensus. *Curr Oncol*. 2018 Oct;25(5):329–337.

4. Song AB, Rosovsky RP, Connors JM, *et al*. Direct oral anticoagulants for treatment and prevention of venous thromboembolism in cancer patients. *Vasc Health Risk Manag*. 2019 Jun 21;15:175–86.

5. Schmid P, Fischer AG, Wuillemin WA. Low molecular weight heparin in patients with renal insufficiency. *Swiss Med Wkly*. 2009 Aug 8; 139(31-32):438–52.

6. Key NS, Khorana AA, Kuderer NM, *et al*. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2020 Feb 10;38(5):496–520.

7. Farge D, Frere C, Connors JM, *et al*. International Initiative on Thrombosis and Cancer (ITAC) advisory panel. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2019 Oct;20(10):e566–e581.

8. Mandala M, Falanga A, Roila F; ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2011 Sep;22 Suppl 6:vi85–92.

9. Amin A, Stemkowski S, Lin J, *et al*. Appropriate thromboprophylaxis in hospitalized cancer patients. *Clin Adv Hematol Oncol*. 2008 Dec;6(12):910–20.

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