Cancer is an important risk factor for venous thromboembolism (VTE). Research has shown that up to 1 in 5 cancer patients experience venous thrombosis.¹ In a large Dutch study that included more than 66,000 cancer patients, researchers found a VTE prevalence of 12.3 per 1,000 patients – more than six times higher than that of the general population (1 to 2 VTEs per 1,000 patients).²

VTE is a significant cause of morbidity and mortality in patients with cancer.³ A study that assessed survival rates for patients with cancer-associated thrombosis (CAT) compared with cancer patients without thrombosis (matched for type of cancer, sex, age, and the year of diagnosis) found that the one-year survival rate was 12% for those who had VTE compared with 36% in control patients.⁴

Thromboembolism is one of the most common causes of death in this vulnerable patient group.⁵ Cancer patients who survive a VTE are at risk for sequelae from the initial event, such as increased bleeding, post-thrombotic syndrome, pulmonary hypertension and recurrent VTE.⁶ For example, cancer-associated thrombosis is associated with a 21% annual risk of recurrent VTE and a 12% annual risk of bleeding complications.⁷ The diagnosis of VTE continues to be a challenge as it is often asymptomatic. In one prospective study of hospitalised patients, the rate of PE was 1%, but the diagnosis was unsuspected in 70% of patients who died from acute PE, as revealed at autopsy.⁸ Yet, VTE is one of the most common preventable causes of cancer inpatient mortality, making prophylaxis critical in this high-risk group. Effective thromboprophylaxis has been shown to reduce morbidity and mortality due to cancer-associated thrombosis. According to international guidelines, low-molecular-weight-heparin (LMWH) is the first choice for the initial and long-term treatment of VTE, as well as for prophylaxis in selected high-risk patients, having largely replaced unfractionated heparin (UFH) and oral vitamin K antagonists such as warfarin.⁹ ¹⁰

Identifying at-risk patients

The pathogenesis of cancer-associated thrombosis (CAT) is complex and multifactorial. The rates of VTE vary widely between different types and stage of cancers. Furthermore, the risk of CAT is influenced by a variety of patient and treatment-related factors, and candidate biomarkers such as blood counts, TF, and P-selectin.¹¹ All of these factors make the prediction of the individual risk of VTE and the identification of patients with cancer that might benefit from thromboprophylaxis major clinical challenges.¹²
CAT risk factors, which are discussed in a separate article, are as follows:\textsuperscript{13}

Patient-related:

- Increased age
- Ethnicity
- Co-morbidities
- Obesity
- Performance status

Treatment-related:

- Chemotherapy, antiangiogenesis agents, hormonal therapy
- Radiation therapy
- Surgery $\geq 60$ mins
- ESAs, transfusions
- Indwelling venous access

Cancer-related:

- Primary site of cancer
- Stage
- Histology
- Time since diagnosis

Biomarkers:

- Platelet count $\geq 350 \times 10^9$/L
- Leukocyte count $> 11 \times 10^9$/L
- Haemoglobin $< 100$g/L

**Khorana risk scoring model**

In 2008, Dr Alok Khorana published what has become a seminal paper in the field of cancer-associated thrombosis, detailing a risk score protocol that helps predict the risk of VTE in ambulatory patients receiving chemotherapy\textsuperscript{14} The Khorana score, as it is known, predicts thrombosis risk based on a collection of simple variables - type of cancer, body mass index (BMI) and complete blood count (platelet, leukocyte, haemoglobin).

Each variable in the score is assigned a value. For example, elevated pre-chemotherapy platelet count of $350 \times 10^9$/L or more, BMI of at least 35 kg/m$^2$, and cancer types such as stomach and pancreas cancer each raise the risk. Cancer patients with a Khorana score of 3 or greater are at high risk for developing blood clots and those with a score of 1 – 2 are at intermediate risk.

The Vienna Cancer and Thrombosis Study subsequently validated this model in another cohort of cancer patients and expanded it with two additional laboratory markers - soluble P-selectin ($\geq 53.1$ ng/ml = VTE risk score 1), and D-dimer ($\geq 1.44$ $\mu$g/ml = VTE risk score 1) - increasing the predictive value of estimating a patient’s risk of CAT.\textsuperscript{15}
In June 2013, the American Society of Clinical Oncology (ASCO) issued updated guidelines affirming the use of this slightly modified Khorana score as a well-established risk calculator for thromboembolism. Specifically, new ASCO guidelines recommend that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter.

**International guidelines on CAT prophylaxis**

Recognising the clinical burden of cancer-associated thrombosis, international guidelines have been issued by the European Society for Medical Oncology (ESMO), ASCO, and the National Comprehensive Cancer Network (NCCN), in which the treatment of CAT is addressed in several patient groups: surgical cancer patients, hospitalised (medical or surgical) cancer patients and also the prevention of thrombosis recurrence in patients with cancer and established VTE.

**Surgical cancer patients:**
Cancer patients undergoing a surgical procedure have twice the risk of postoperative VTE as patients who undergo surgery for benign diseases. In addition, after surgery for cancer, patients with VTE experienced a 5.3-fold greater chance of mortality than patients without. In this high-risk patient group, ‘the role of prophylaxis is unquestionable’.

The Enoxaparin and Cancer (ENOXACAN) trial in patients undergoing curative abdominal or pelvic surgery for cancer showed that, given two hours preoperatively and for approximately 10 days post-surgery, the LMWH enoxaparin at 40 mg once daily is as effective and well tolerated as UFH at 5,000 IU three times daily in reducing the incidence of thromboembolic complications post-surgery, with no significant difference in the incidence of bleeding between the two regimens. ASCO and other international guidelines recommended that patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days.

Laporte et al, found that the LWMH tinzaparin is a valuable option for long-term treatment of VTE in patients in whom vitamin K antagonists (VKA) are contraindicated or difficult to monitor. Tinzaparin may have a more favorable benefit-risk ratio than VKA in patients with cancer and VTE. This analysis of five randomised controlled studies on long-term tinzaparin in patients with VTE investigated whether long-term curative doses of tinzaparin is a valuable alternative to VKA for the treatment of symptomatic VTE, especially in patients with cancer who are at higher risk of recurrence and bleeding. In cancer patients, a non-significant 38% VTE risk reduction in favour of tinzaparin was observed on treatment (RR=0.62 [0.30; 1.31]), although the difference was significant at the end of follow-up at one year (RR=0.40 [0.19; 0.82], p<0.01). There was no significant difference in the incidence of major bleeding.

Extended prophylaxis to four weeks post-surgery was associated with a greater than 50% reduction in venographic VTE in patients undergoing major abdominal surgery. The FAME study compared the efficacy of one week versus four weeks of thromboprophylaxis with LMWH (dalteparin sodium 5000 IU once daily) in major abdominal surgery patients. Researchers found that the cumulative incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis (29/178 patients) to 7.3% after prolonged thromboprophylaxis (12/165) (relative risk reduction 55%; 95% CI 15-76; P=0.012), with no increase in bleeding events. In addition, an individual patient data meta-analysis of the two studies of the LMWH tinzaparin confirmed a reduction in risk with extended prophylaxis.
As a result, ASCO, ESMO and NCCN guidelines agree that extending postoperative prophylaxis up to four weeks should be considered in those with high-risk features (particularly those undergoing major abdominal or pelvic surgery).

**Hospitalised patients:**

Hospitalised patients are at greater risk for developing VTE and this risk is further increased in patients with cancer. However, the literature indicates that these patients are often inadequately anticoagulated, despite strong recommendations for prophylaxis. For example, the International Medical Prophylaxis Registry on Venous Thromboembolism (IMPROVE) registry, which was designed to assess thromboprophylaxis patterns, found that only 45% of eligible cancer patients received prophylaxis. Clinical studies have demonstrated the effectiveness of thromboprophylaxis in reducing VTE events in hospitalised cancer patients: the MEDENOX trial recorded a 63% relative risk reduction (RRR) in patients receiving enoxaparin, compared to those receiving placebo; there was a 45% RRR in patients receiving dalteparin, compared to placebo, in the PREVENT study; and, in the ARTEMIS trial, a RRR of 47% was confirmed in the fondaparinux group, compared to the placebo group.

While international guidelines agree that hospitalised patients are at increased risk of thrombosis, they differ on the specifics of which patients should receive pharmacologic thromboprophylaxis (although there is agreement that it should only be administered in the absence of bleeding or other contraindications).

ACSO recommend that pharmacologic thromboprophylaxis should definitely be given to hospitalised patients who have active malignancy and acute medical illness or reduced mobility; should be considered in hospitalised patients without additional risk factors; and is not recommended in patients admitted for minor procedures or short chemotherapy infusion, or in patients undergoing stem-cell/bone marrow transplantation.

The NCCN panel of experts recommend the use of prophylactic anticoagulation therapy in high-risk inpatients, and should be considered in other outpatients at risk. The LMWHs, fondaparinux, and subcutaneous UFH (5,000 units, three times daily) are category 1 options for inpatient prophylactic therapy.

The ESMO guidelines specify prophylaxis with UFH, LMWH or fondaparinux in hospitalised cancer patients confined to bed with an acute medical complication. However, extensive, routine prophylaxis for advanced cancer patients receiving chemotherapy is not recommended, but may be considered in high-risk ambulatory cancer patients. Prophylaxis in cancer patients receiving adjuvant chemotherapy and/or hormone therapy is not recommended.

With regard to thromboprophylaxis for cancer patients with a central venous access device (CVAD), both the ESMO and NCCN guidelines did not recommend extensive, routine prophylaxis to prevent CVC-related VTE, while the ASCO guidelines made no specific recommendation.

**References**


