Since French internist Armand Trousseau reported the occurrence of ‘mysterious’ thrombotic disorders in cancer patients in the mid-19th century, the link between cancer and hypercoagulable states has been confirmed and well documented. Cancer alone is associated with a more than four-fold risk of thrombosis.¹

The prothrombotic state of malignancy occurs due to the ability of tumour cells to activate the coagulation system, placing cancer patients at an elevated risk of venous thromboembolism (VTE; deep vein thrombosis [DVT] and pulmonary embolism [PE]). This hypercoagulation is responsible for a significant percentage of mortality and morbidity in cancer patients.²

**Prognosis**

Research has confirmed that patients with concurrent VTE and malignancy have a more than threefold higher risk of recurrent thromboembolic disease and death than patients with DVT/PE without malignancy.³ Thromboembolic events are the second leading cause of death in cancer patients receiving chemotherapy (after cancer itself) and, even among patients who survive an episode of VTE, complications such as recurrent VTE, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension are common, costly, and have a profound impact on the patient's quality of life.⁴

Compounding the underlying pathophysiologic propensity for coagulation, patients with cancer also have a number of extrinsic factors that increase the thrombotic risk. These include surgery, anti-cancer therapies (chemotherapeutic and antiangiogenic agents), hormonal therapy, long-term immobilisation, central venous catheters, cancer type, and advanced disease stage.

For example, a study in lung cancer patients found the risk of VTE was 30% higher among patients undergoing chemotherapy (compared to those not receiving chemotherapy),⁵ and VTE was responsible for nearly half (46.3%) of all deaths in patients undergoing cancer surgery.⁶
Complications

VTE recurrence
Research has demonstrated that patients who develop cancer-associated thrombosis have a three-fold higher risk for recurrent VTE than patients who had an initial VTE in the absence of malignancy. Approximately 25% of cancer patients with VTE require readmission because of bleeding or recurrent VTE.

Post-thrombotic syndrome
An estimated 23% - 60% of patients who develop DVT will develop post-thrombotic syndrome (PTS), frequently occurring within two years of the DVT episode. PTS is a chronic, potentially disabling condition, manifesting as swelling, pain, oedema, fibrosis, and venous ectasia.

A blood clot in a leg vein can cause inflammation and block blood flow, causing damage to the tiny valves that control the direction of blood flow. The damaged valves become leaky, allowing fluid to pool around the ankles, and the leg becomes painful, red, and swollen. As PTS worsens, poor blood flow in the leg can cause painful leg ulcers that require long-term nursing care.

Chronic thromboembolic pulmonary hypertension
Chronic thromboembolic pulmonary hypertension (CTPH) - a form of pulmonary hypertension caused by old blood clots in the lungs (pulmonary embolism) - is associated with considerable morbidity and mortality. This condition was believed to be a rare complication of PE, arising in approximately 1% of patients, but a recent study found that CTPH is relatively common. This prospective, long-term, follow-up study found that the cumulative incidence of symptomatic CTPH was up to 4% at two years post-PE event.

Incidental thrombosis
Increasingly, VTE is being diagnosed as an incidental finding on CT scans ordered for other indications, such as staging or restaging of cancer. In a study of gastrointestinal cancer patients, half of all DVTs and over 35% of PE were incidentally discovered. Another study found that 44% of all venous and arterial thromboembolic events in cancer patients receiving chemotherapy were incidental.

Occult cancer
Not only is VTE a common complication in patients with cancer, it may be the first manifestation of cancer. Almost one in ten patients who present with unprovoked or idiopathic VTE will be diagnosed with cancer within the first two years after their thrombotic event. It is reported that, in cases where cancer is diagnosed after an episode of VTE, the cancer is often advanced (approximately 40% have metastatic cancer at diagnosis) and the outcome is very poor, with a one-year survival of only 12%.
Research has suggested that an initial assessment consisting of a comprehensive medical history, physical examination and basic laboratory testing will detect a large proportion of occult cancers in patients with idiopathic VTE. In a study of almost 900 patients with acute VTE, an initial routine clinical evaluation for malignancy identified cancer in 4% of patients; a further limited diagnostic work-up identified another 1.6% of cancers, with a one-year follow-up revealing cancer in another 1.7% of patients. The authors concluded that routine examination identified more than half of the malignancies, predominantly at an early stage.\textsuperscript{18}

NICE guidelines (CG144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing) recommend that all patients diagnosed with unprovoked DVT or PE, who are not already known to have cancer, should be offered the following investigations for cancer:

- A physical examination (guided by the patient’s full history) and
- A chest Xray and
- Blood tests (full blood count, serum calcium and liver function tests) and
- Urinalysis.

In addition, physicians should consider further investigations for cancer with an abdominopelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation.\textsuperscript{19}

**Two-way clinical association**

A growing body of data has confirmed a two-way clinical association between cancer and thrombosis. Research has shown that malignant tumour growth can trigger activation of the coagulation cascade, which not only leads to a prothrombotic environment that manifests as VTE but also has a profound effect on tumour cell behaviour, eliciting or enhancing tumour cell survival, invasion, metastasis, and angiogenesis.\textsuperscript{20}

Supporting this theory that activation of the coagulation system contributes to tumour aggressiveness and vice versa, various authors have described a significant correlation between thrombosis and a poorer cancer prognosis. A Danish study revealed that a diagnosis of DVT or PE within one year of a cancer diagnosis is a significant predictor of death. Even when patients were matched by the type of cancer, age, sex, and year of diagnosis, the first-year survival rate was 12% in cancer patients with VTE, compared to 36% in cancer patients without a diagnosis of thromboembolic events.\textsuperscript{21}

As antithrombotic therapy has proven beneficial effects on survival in patients with cancer in terms of treatment and prevention of VTE, clinical evidence spanning thirty years of antithrombotic agents suggests their administration to cancer patients may also have a direct effect on tumours and influence survival.
In the Veterans Administration (VA) Co-operative trial, the potential benefit of warfarin therapy in cancer was evaluated. Patients with lung-colon, head and neck, and prostate cancer were randomised to either warfarin in addition to standard treatment, or standard treatment alone for a period of 26 weeks. The main outcome showed no significant difference between the two arms, however, among the 50 patients with small-cell lung cancer (SCLC) there was significant improvements in time to disease progression and in overall survival.\textsuperscript{22}

A follow up study targeting almost 330 SCLC patients receiving chemotherapy with or without warfarin therapy reported a statistically significant advantage in the warfarin group in achieving complete or partial responses, and an improvement in overall survival.\textsuperscript{23}

More recently, thromboprophylaxis with low molecular weight heparin (LMWH) has demonstrated tangible anticancer effects in several clinical trials encompassing a wide array of malignancies.\textsuperscript{24}

References