


## Updated review on malignancy-associated venous thromboembolism: Pathogenesis and comparison between various therapeutic modalities

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### ABSTRACT

Venous thromboembolism (VTE) is one of the life-threatening complications in cancer patients, the incidence of which is affected by the patient and malignancy-related variables. Location, type, therapeutic route, stage, grade, and non-supportive treatment of the cancer are the most important VTE risk factors. Patient age, ethnicity, and concomitant genetic or acquired comorbidities or thrombophilias are known risk factors for VTE in cancer. All high-risk cancer patients admitted to hospitals or treated as outpatients should receive VTE prophylaxis. Low molecular weight heparin is the main treatment for active malignant VTE. Vitamin K antagonists and non-Vitamin K-dependent oral anticoagulants are used in stable, non-bleeding cancer patients. Anticoagulation should be continued until the cancer is treated or at least controlled. Over the past two decades, randomized clinical and observational trials have improved the pathogenesis and therapeutic knowledge of VTE, but many challenges remain. The lack of an optimal primary prophylaxis method for inpatients and outpatients in oncology and the care of cancer-associated VTE in standard and high-bleeding risk groups are examples for which more clinical research on cancer-associated thrombosis is necessary to address these issues. In this review, we describe the pathogenesis, factors that increase the risk of VTE, and the comparison between the effectiveness of available anticoagulants in the treatment and prevention of VTE in cancer patients.

**Key words:** Anticoagulation in malignancy, Cancer and direct oral anticoagulant, Low molecular weight heparin in malignancy, Venous thromboembolism in cancer, Vitamin K antagonist in cancer, Warfarin in malignancy

An imbalance in the natural process of blood clotting can significantly increase the risk of developing either a thrombosis or excessive bleeding [1]. In certain medical conditions such as disseminated intravascular coagulopathy or in patients with underlying cancer who develop a coagulopathy, there is a simultaneous increased risk of both thrombosis and bleeding. It is crucial to be vigilant and take necessary measures to prevent such complications in patients with a higher risk of thrombosis and bleeding.

Arterial and venous thromboembolism (VTE) can occur in cancer patients. The term “VTE” includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), which are common in cancer, and its management justifies the focus of this review. Arterial and venous thrombi can restrict normal blood flow and lead to deleterious clinical consequences. The ability of blood to flow freely through arteries and veins is determined by

complex homeostasis achieved by interactions between platelets, plasma proteins, inflammatory factors, cytokines, coagulation factors, and the integrity of the endothelial layer of veins and arteries [1]. Pregnancy, hormone therapy, contraceptives, and obesity are known to increase the risk of VTEs [2,3]. Moreover, the cumulative incidence of VTE after cancer diagnosis was found to be 11.1-fold higher than in patients without cancer [4].

In epidemiological research, VTE is often classified as either provoked or unprovoked. Provoked VTEs are the result of certain causes that occur during the 3 months before, such as immobility, trauma, surgery, malignancy, or hospitalization [5]. On the other hand, unprovoked occurrences happen without evidence of these causes being present [6,7]. The categorization of provoked or unprovoked VTEs, although beneficial for both epidemiological and therapeutic purposes is a subject of controversy [6,7]. Due to the complex nature of VTE, it might be difficult (or impossible) to pinpoint a specific trait that caused VTE or to classify a series of lesser thrombotic incidents that culminated in a VTE event

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#### Access this article online

Received - 21 March 2024  
Initial Review - 25 March 2024  
Accepted - 11 April 2024

DOI: 10.32677/yjm.v3i1.4547

#### Quick Response code



as unprovoked. The 2019 guidelines from the European Society of Cardiology/European Respiratory Society for diagnosing and treating acute PE did not use the terms “provoked” and “unprovoked.” Instead, they emphasized that the long-term VTE recurrence risk is based on the underlying factors, with a risk of <3% per year considered low, 3–8% per year considered intermediate, and over 8% per year considered high [8].

In this review, we aim to discuss in detail the pathogenesis and factors that increase VTE, comparison between the effectiveness of available anticoagulants in the treatment and prevention of VTE, and the anticancer effects of anticoagulants currently used. To achieve the purpose of the review, various phrases and keywords (anticoagulation in malignancies, VTEs prevention in cancer, cancer-associated thrombosis, VTEs in malignancy, direct oral anticoagulant [DOAC], vitamin K antagonist [VKA], and VTE) were used to search PubMed, EMBASE, Scopus, Google Scholar, and Google search engine, looking for a recently published reviews and original articles on VTE in malignancy for the period between 1982 and 2024.

### VTE EPIDEMIOLOGY AND EFFECTS ON CANCER PATIENTS' OUTCOME

VTE is estimated to affect 1–2 persons/1000 person-years in Europe and the US, with lesser rates in other world regions, despite the absence of VTE surveillance systems [5]. VTE is a frequent illness affecting >1 in 12 subjects during their lifetime in the Western World [5]. An estimated 4–20% of cancer patients are likely to have VTE at some point, with the greatest occurrence rate seen shortly after diagnosis. Every year, 0.5% of individuals diagnosed with cancer will develop thrombosis, whereas the incidence rate in the general population is 0.1% [9]. VTE absolute incidence across all cancer types was 13.9/1000 person-years in Britain [10,11]. In hepatic and pancreatic malignancies, an East Asian study found a cancer-associated VTE incidence of 9.9/1000 person-years [12]. Moreover, about a fifth of subjects who develop a VTE attack die within 1 year and the VTE in this group is usually due to a provoking condition.

VTE complications are more frequent among survivors [13]. Cancer patients make up around 20% of all VTE cases [14,15]. Cancer patients have a 5–7-fold higher likelihood of getting VTE [16]. In addition, individuals who acquire VTE at the time of cancer diagnosis or within the 1<sup>st</sup> year are likely to have a notably worse prognosis compared to cancer patients who do not experience VTE [17]. The occurrence of VTE in cancer patients is a significant and detrimental complication that harms their quality of life and decreases their chances of survival [18].

According to research, individuals with cancer had a 3 times greater chance of experiencing recurrent VTE and a 2 times greater chance of experiencing bleeding linked with anticoagulant treatment [19]. It was reported that gastrointestinal (GI) cancer patients have a higher VTE rate than non-GI cancer patients [20]. A study described that 220 GI cancer patients (27.3%) experienced either single or recurrent VTE attacks, with DVT accounting for 38.6% and PE for 20.5% [20].

VTE is linked to a significant burden of morbidities caused by enduring sequelae, including blood coagulation recurrence, post-thrombotic syndrome, and post-PE syndrome. Although there is awareness of several risk factors and triggers, about 33% of VTE incidents occur without any apparent inciting factor (unprovoked) [21]. Death occurs in approximately 6% of DVT cases and 12% of PE cases [22]. Unfortunately, VTE is one of the primary causes of mortality among cancer patients [23]. Cancer patients who also have VTE face a risk of death that is 10 times higher compared to individuals who just have VTE, and 4 times higher compared to cancer patients who do not have VTE [24]. VTE is the second cause of mortality in individuals with cancer [23,25]. Hence, it is crucial to prioritize VTE prevention and treatment for effective management of patients with cancer.

### FACTORS AFFECTING VTE PATHOGENESIS IN MALIGNANCY

Table 1 summarizes the factors influencing the pathogenesis of VTE, particularly in malignancies. The incidence of VTE in malignancies is influenced by factors such as the primary location of the tumor, its stage, and histological features. The highest-risk cancers include pancreatic, lung, stomach, and brain cancers, as well as hematologic malignancies, while the lowest-risk cancers include prostate and breast cancers [26–29]. The likelihood of developing VTE increases proportionally to the severity of the cancer. The adjusted relative risk of VTE hospitalization in Danish population-based research was 2.9, 2.9, 7.5, and 17.1 for stage 1, 2, 3, and 4 cancers, respectively [30]. Higher-grade tumors (grades 3 and 4) have twice the incidence of VTE compared to lower-grade tumors (grades 1 and 2) [31]. The incidence of VTE varies over the course of the disease in cancer patients. Within the first 6 months after diagnosis of colorectal cancer, the probability of developing VTE is 5 cases/100 person-years. This risk decreases to 1.4 cases/100 person-years between 7 and 12 months after diagnosis and decreases further to 0.6/100 person-years between 13 and 24 months after initial presentation [32]. Cancer treatment also affects a patient's susceptibility to VTE. For example, the susceptibility to VTE in oncologic surgery is

**Table 1: Patient, cancer, comorbidities, and therapy types used are risk factors for venous thromboembolism**

Risk factors	Predictors of venous thromboembolism
Patient-related factors	Age, gender, skin color, origin, body mass index, and thrombophilia-diseased patients.
Cancer-related factors	Cancer type, nature, localized or spread at presentation, stage, histological characteristics, and severity of the cancer.
Comorbidities factors	Infection, renal disease, arterial thromboembolism, pulmonary disease, and anemia.
Chemotherapy-related factors	Inpatient or ambulatory, drug types used in chemotherapy, central, and peripheral catheter insertion.
Surgical treatment-related factor	Surgery type, tumor site, in-bed duration, prolonged admission, and longer immobility.

1.7 times higher than in non-cancer surgery [33]. In a population-based observational analysis of breast cancer, it was found that undergoing surgery was linked to a 2.2-fold higher VTE risk in the 1<sup>st</sup> month after being discharged. However, this risk decreased in the following months. The Rochester Epidemiology Project found that chemotherapy was linked to a 1.8-fold uprise in VTE incidence [34].

Chemotherapy in breast cancer patients was found to be linked to a 10.8-fold increase of VTE during treatment, although this risk returned to normal levels 3 months after treatment was finished. The use of hormonal therapy was found to be linked to 2.4 times higher VTE risk within the initial 3 months of treatment with the degree of risk varying depending on the specific medication used. Tamoxifen exhibited a 5.5-fold higher risk, while aromatase inhibitors did not show any association with VTE. Treatment plans that include thalidomide or lenalidomide along with high-dose dexamethasone, with or without multi-agent chemotherapy, were associated with a higher feasibility of developing VTE. On the other hand, treatment plans that involve low-dose dexamethasone or bortezomib are associated with less VTE risk [35]. Although early research indicated that the bevacizumab (the vascular endothelial growth factor receptor [VEGFR] antagonist, that causes vasoconstriction of tumor supplying blood vessel) use was linked to a higher likelihood of VTE, a recent meta-analysis that considered the duration of treatment found no evidence of an increased risk [36]. There has been no observed rise in VTE when using other inhibitors of VEGFR [37]. Nevertheless, monoclonal antibodies that target the epidermal growth factor (EGF) receptor (EGFR) have been linked to 2 times greater VTE risk, whereas, EGFR tyrosine kinase inhibitors have not shown this association [38]. The EGF binds to the EGFR, dimerizing, activating, autophosphorylating it, and activating signaling pathways that promote proliferation [39]. The utilization of erythropoiesis stimulatory agents generally heightens the tendency of VTE [40]. Surgically treated cancer patients have a higher risk of developing VTEs due to varied reasons, including immobility, vessel injuries, surgical approach, and prolonged bedbound periods. Furthermore, in cancer, VTE

risk was notably elevated when surgery was conducted within the 2 months following chemotherapy treatment [28].

Individual patient features also have an impact on VTE risk. Hospitalized cancer patients are aged  $\geq 65$  years, especially females have shown a slightly higher tendency of developing VTE. Black patients had a 20% higher risk, while Asian patients had a reduced risk [40]. Ashrani *et al.* observed that obesity, defined as a body mass index of  $35 \text{ kg/m}^2$  was linked to a fourfold rise in risk [41]. The large case-control study on VT (MEGA case-control study) found that individuals with factor V Leiden heterozygosity had a 100% increased VTE incidence [14]. Comorbid disorders such as infection, renal disease, arterial thromboembolism, pulmonary disease, and anemia increase the VTE rate in cancer patients [42].

### PATHOPHYSIOLOGY OF VTE

Fig. 1 describes the pathophysiology of thromboembolism in different clinical settings. Thrombosis is characterized by the obstruction of the circulatory system's normal blood flow due to the formation of a thrombus within a blood vessel. A thrombus is composed of a plug-forming aggregate of platelets and red blood cells and a fibrin protein mesh that has been cross-linked. The underlying mechanisms of thrombosis are significantly influenced by Virchow's triad, which consists of endothelial injury or malfunction, hypercoagulability, and blood stasis inside the veins or arteries. The vascular wall's damage or malfunction results in the generation of pro-inflammatory, cytokines, prothrombotic, the growth of adhesion molecules, an elevation in tissue factor availability, and intensified platelet activation. Cytokines trigger an inflammatory interaction between leukocytes and endothelial cells. Thrombophilia patients (deficits in protein C and S, anticardiolipin antibody, and antithrombin III) are more susceptible for developing thrombosis. Recent surgery, inflammation, pregnancy, infection, estrogen-containing medications, morbid obesity, or smoking increase further thrombosis risk.

Inflammation is a natural response of the body to undesirable stimuli, such as external pathogens, infection, or damage to the

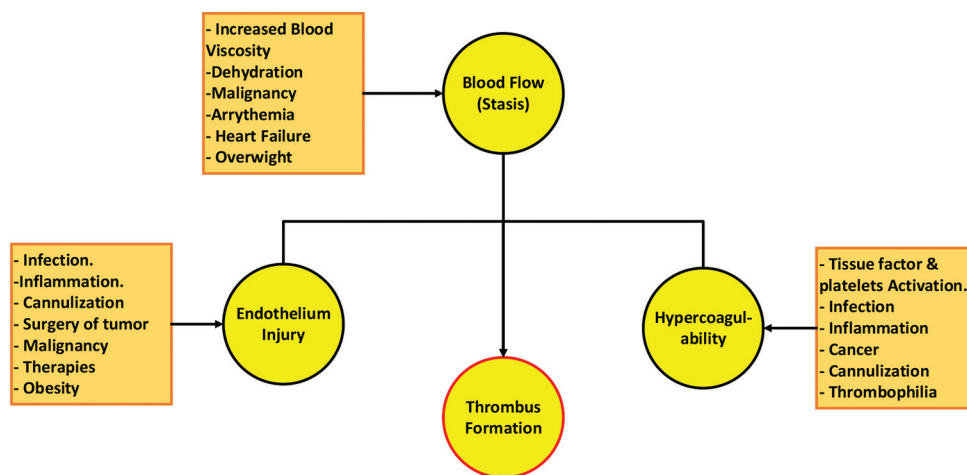


Figure 1: Pathogenesis of thrombus formation

endothelium cells. This response may occur in acute conditions, such as trauma or surgery, and chronic conditions, such as underlying inflammatory illnesses or peripheral vascular disease. Due to these stimuli, endothelial cells and leukocytes become activated, leading to adhesion molecule formation that ultimately triggers the development of blood clots [43]. The body's innate anticoagulants (protein C and S and antithrombin-III) inhibit the development of blood clots through an intricate regulatory process that ensures stability intravascularly. Furthermore, physiologically, the body has continued thrombolysis processes that lysis the small thromboses. Imbalances in the process of clot formation and dissolution cause extensive intravascular thrombosis.

VTE often originates in the sinus of the veins' valves, where distinct characteristics of the valves increase the blood clot formation likelihood. These factors include aberrant and diminished circulation of blood, decreased shear stress, and hypoxia resulting in an endothelium that is intact but not functioning properly [44]. Furthermore, platelets and leukocytes tend to get ensnared in valve pockets [45]. All these mechanisms that engage in prevention and thrombus formation are altered by tumors in cancer patients. For example, tumor overgrowth, increased cellular part of the blood, and abnormal increase of blood protein content all may exert pressure on veins, delaying blood flow, and injuring the vascular endothelium, leading to venous stasis, which in turn promotes the formation of thrombosis.

Myocardial infarction and coronary heart disease prevalence is high in cancer [46]. The uppermost prevalence was reported during the first 6–12 months after cancer diagnosis [47–49], and the risk remains high even after 10 years [49]. Arterial thrombosis, along with the creation of microthrombi, usually begins when lipid plaques build up in the arterial walls, triggering the activation of platelets and inflammatory cells, as in coronary heart disease [50]. Platelets have a greater impact on arterial thrombosis formation compared to venous thrombosis formation. Therefore, antiplatelet medications are essential in preventing and treating arterial thrombosis. The early lipid plaques progress into fibrous plaques (atherosclerosis). As a consequence, the fibrous plaque has the potential to rupture and detach away some plaques of the arterial endothelium, resulting in the discharge of extra pro-coagulating substances [50]. Atherosclerosis facilitates the stimulation of platelets, resulting in their adherence and aggregation, ultimately leading to clot formation [43].

### **VTE Risks and Chemotherapy**

To prevent VTE, it is crucial to identify high-risk cancer patients who might benefit from thromboprophylaxis. The prevalence of symptomatic VTE ranging from 5% to 7% is undoubtedly comparable to or even higher than that observed in hospitalized or post-operative patients, where VTE prophylaxis has demonstrated remarkable efficacy [51,52]. Risk assessment models (RAMs) have been used clinically to assess DVT and PE risk in other populations [53,54], which do not apply to cancer patients [55].

A prevalent complication of cancer and antineoplastic treatment is the occurrence and recurrence of VTE.

More studies have identified associated risk factors with cancer-associated VTE. These factors comprise the primary cancer origin and location, the existence of metastases, and the utilization of antineoplastic treatments such as chemotherapy, hormonal therapy, surgical procedures, and erythropoiesis-stimulating agents [14,56,57]. Active-treatment cancer patients have the highest VTE development risk. Chemotherapy increased thrombosis risk by 6.5-fold, whereas cancer patients have a 4.1-fold VTE-increased risk, according to a population-based study [58]. Interestingly, it was reported that breast cancer patients have a higher VTE rate, especially stage II, which reduces significantly after chemotherapy completion [59].

Significant ramifications ensue for cancer individuals who develop VTE. These include the need for ongoing anticoagulation, potential chemotherapy delivery delays, a heightened likelihood of recurrent VTE, increased bleeding complications risk while on anticoagulants, diminished life quality, and increased health-care cost [60]. Furthermore, even after the adjustment to the disease stage, VTE increases mortality by twofold or more compared to patients who had cancer without VTE [61]. Thromboembolism is the principal cause of mortality among cancer patients [23].

In several high-risk populations, including hospitalized patients and those undergoing surgery, primary VTE prophylaxis reduces fatal PE and DVT [62,63]. Effective prophylaxis and cancer patient identification at risk for VTE could lead to improvements in cancer-related morbidity and mortality, cancer therapy delivery, life quality, and savings in health-care costs. Cancer outpatients who met specific risk factors, including lung cancer, metastatic breast cancer, and intravenous catheter presence have participated in clinical trials involving thromboprophylaxis [64,65]. However, 19 of these studies have been unsuccessful in demonstrating the benefit of VTE primary thromboprophylaxis. Present consensus guidelines do not advise prophylaxis for outpatients with cancer [66].

Furthermore, another important precipitating risk factor that increases VTE in malignancy is the route of chemotherapy administration. Chemotherapy is usually given through a small cannula in the peripheral vein. However, the peripheral veins are small and usually damage quickly due to repeated puncturing and chemotherapy. Hence, central vein catheter (CVC) and peripheral vein catheter (PICC) are inserted and used for chemotherapy. These two modalities make the infusion of chemotherapy agents more accessible and more convenient, with less damage to veins, less oozing risk of chemotherapy, and painless chemotherapy sessions.

### **Central Venous Catheter Thromboembolism in Cancer**

Central and peripherally inserted PICC lines are commonly used to administer chemotherapy in cancer patients. Peripheral PICC lines have a higher rate of thrombosis compared to central venous lines [67]. A CVC is required to enable chemotherapy for various cancer patients. Besides the increased infection rate,

arterial canalization, hemorrhage, and hematomas, central venous catheterization is linked with catheter-induced thrombosis and thromboembolism risk, especially in cancer patients [68]. These can lead to complications that significantly promote morbidity and death in cancer individuals [69]. The most common non-infectious consequence linked to central line use is thrombosis, resulting in chemotherapy delay [70]. Central line vein thrombosis ranges between 5% and 18% [71,72]. Another report revealed that catheter-related thrombosis clinical evidence is seen in around 4–8% of cancer patients [73].

The average occurrence rate of catheter-related thrombosis, identified using either echography or Doppler, falls within the range of 12–14%, exhibiting a significant negative projecting value of around 95%. At present, there is no recognized thromboprophylaxis for PICC or CVC thrombosis despite its high occurrence and significant medico-economic impact. Catheter related thrombosis often manifests promptly after catheter placement, mostly during the first 7 days and universally within the initial month post-insertion. To avoid catheter-linked thrombosis, it is imperative to consider various local and systemic risk factors. This may be achieved by ensuring proper catheter insertion and maintenance protocols are followed consistently. Routine recommendations do not support the regular use of primary pharmacological thromboprophylaxis to prevent catheter-linked thrombosis. However, it may be explored in certain instances [70].

Meta-analyses indicate that the incidence of both asymptomatic and symptomatic catheter-linked thrombosis may be reduced by around 55–60% when using either VKAs or Low molecular weight heparins (LMWHs) without a significant bleeding risk increase. The efficacy of this type of VTE prophylaxis is contingent on initiation before the implantation of the central venous catheter, at dosages intended for prophylaxis, and subsequent continuation at doses below therapeutic levels [73], with accepting the risk of bleeding during insertion.

A considerable number of researchers have endeavored to ascertain efficacious catheter-related thrombosis prophylactic regimes. At first glance, an open randomized study indicated that the administration of low-dose warfarin (1 mg/day) might substantially diminish the occurrence of catheter-related thrombosis among cancer patients (from 37.5% to 9.5%) [74]. Nevertheless, several subsequent randomized controlled trials (RCTs) have been unable to establish any protective effect associated with fixed low-dose warfarin [64,73,75]. Similarly, RCTs utilizing LMWH showed comparable results to low-dose warfarin. In comparison to no treatment, dalteparin 2500 IU single daily dose substantially decreased CVC-related thrombosis, according to a small open RCT ( $p=0.002$ ) [76]. Nevertheless, despite subsequent larger RCTs utilizing nadroparin, dalteparin, and enoxaparin DVT prophylactic regimens, there were no reductions in catheter-related thrombosis observed [65,77-79]. A significant diminution in catheter-related thrombosis was observed in pediatric and adults following bone marrow transplant in a small open-label study of continuous infusion unfractionated

heparin ( $p=0.03$ ) [80]. Lavau-Denes *et al.* conducted a study involving 420 patients and observed that those treated with a prophylactic dose of VKA or LMWH had a lower catheter-related thrombosis incidence (8.1%) compared to those who had not received any anticoagulation (14.8%) [81].

Anticoagulant CVC thromboprophylaxis has been the subject of meta-analyses [81-84]. As the all-anticoagulant modalities data were combined, Akl *et al.* observed a 44% relative risk drop in symptomatic CVC-associated thrombosis episodes, whereas other studies had not observed such a drop [84]. A study observed that LMWH and VKA reduced the relative incidence of symptomatic and asymptomatic catheter-related thrombosis by 63% and 28%, respectively [85]. In contrast, others did not find this information, possibly because their inclusion criteria differed [86,87]. A meta-analysis review reported that the relative reduction in the risk of catheter-related thrombosis was observed more with LMWH in symptomatic events (–52%) and exclusively with VKA in asymptomatic events (57%) [85]. There was no evidence of superiority in any antithrombotic regimen (e.g., VKAs vs. LMWH) according to any meta-analysis. There were no noted disparities in significant hemorrhage or mortality rates between the control group and the patients who were administered anticoagulants. Therefore, it is not recommended to administer pharmacologic prophylaxis on a routine basis to prevent thrombosis that is associated with CVCs [73,88-90]. Although most meta-analyses found prophylactic anticoagulation to be beneficial, few clinical trials observed a reduced catheter-related thrombosis rate. Dejectedly, the findings of different large, randomized studies conducted to date may have two significant limitations. The dosage of the anticoagulant is the initial restriction. Young *et al.* reported that 1590 patients with malignancy and CVC thrombosis received 1 mg/day warfarin compared to no warfarin. They did not find a significant decline in the catheter-associated thrombosis occurrence rate that was confirmed radiographically as symptomatic ( $p=0.98$ ) [75]. However, dose-adjusted warfarin significantly decreased the incidence of such complications ( $p=0.002$ ), although the cost of this was an increase in major bleeding (MB) complications ( $p=0.04$ ). The delayed and highly variable initiation of antithrombotic prophylaxis after catheter insertion constitutes the second constraint. Hence, the potential lack of benefit observed by the authors may be credited to the administration of prophylactic medication after the onset of the pathophysiologic processes that precipitated thrombosis. However, further studies are required to assess the benefit of warfarin in the prevention of CVC thrombosis.

While precise data regarding the pathogeny of catheter-related thrombosis are lacking, it has been underscored that cancer patients face a significantly heightened risk for this complication in the initial hours or days following the insertion of a central venous catheter [77,91]. Catheter insertion appears to be the most significant risk factor for catheter-associated thrombosis [73,88,92-94]. This is likely due to endothelial injury or direct blood vessel wall trauma, which increases thrombus likelihood, especially in the hours or days following the insertion

of a central venous catheter when the repair processes are not yet complete [77]. As De Cicco *et al.* demonstrated, this evidence emphasizes the critical nature of initiating antithrombotic prophylaxis before the insertion of CVC. They studied 348 cancer patients who were assigned to receive either 5000 IU dalteparin or 1 mg acenocoumarin daily, 3 days and 2 h preceding the insertion of the central venous catheter, or no anticoagulant treatment [77]. Following catheter insertion, VKA and LMWH therapy lasted for 8 days [77]. The anticoagulated group (on VKA and LMWH) had a lower catheter-related thrombosis incidence on days 8 and 30 after CVC insertion (21.9% and 40.0%, respectively) compared to the observation group (52.6%;  $p < 0.01$ ). The higher efficacy of acenocoumarin in comparison to dalteparin may have been attributed to an overdose of VKA, as 10% of acenocoumarin patients group exhibited an INR value  $> 1.5$  [77].

The dosages of prophylactic agents utilized in this investigation were deemed safe, as no significant hemorrhaging occurred. Similarly, the administration of antiplatelet agents or anticoagulants before catheter insertion was found to be beneficial in two studies [75,95]. According to the WARP study, warfarin administration could commence 3 days before the insertion of a central venous catheter to ensure sufficient drug exposure in the immediate post-insertion phase. This factor potentially contributed to the favorable outcomes observed in this trial [73,75]. In the ONCOlogie et Chambres ImPlantables (ONCOICIP) study, 3032 cancer patients were monitored for 12 months [95]. It was observed that patients who had used continuous antiplatelet treatment at the outset had a reduced catheter-related thrombosis incidence [95]. Although there are conflicting reports about the benefit of anticoagulation before or after the CVC insertion, it seems that further studies need to clarify whether and when to start anticoagulation and which anticoagulant to give, which needs further research projects.

## ANTICANCER EFFECTS OF ANTICOAGULANTS

Patients with advanced cancer and metastasis sometimes need to be bedridden for extended periods. This greatly heightens the likelihood of developing VTEs [96]. There has been an increased interest in the potential effects of anticoagulants for treating cancer and complication prevention. This is because there are connections between blood clotting and the biology and prognosis of cancer [97]. Specific angiogenic mechanisms are promoted in cancer development as a result of cellular interactions, localized oxygen deprivation, and the presence of specific cytokines and growth factors [16,97]. It was observed that anticoagulants might decrease 5-fluorouracil effectiveness, highlighting potential flaws in treating VTE in these types of patients [97].

### VKA Anticancer Effect

VKA use showed antiproliferative properties in pancreatic cancer [98]. In an investigation, Coumarin, a warfarin component, inhibits tumor cell growth and migration [99]. Vitro studies

showed anti-adhesive VKA actions and decreased breast cancer metastasis [100]. Human observational studies presented that warfarin reduces the overall incidence of lung, prostate, colon, and breast cancers [101]. Moreover, O'Rourke *et al.* reported an association between warfarin pre-diagnostic use and cancer-specific mortality in breast, lung, prostate, and colorectal cancer [102]. Warfarin functions as an antiproliferative and antimigratory agent achieved by inhibiting the  $\gamma$ -carboxylation of the Gla-domain on gamma-carboxylglutamic acid-6 (Gas6). This leads to reduced activation of receptors and diminished Axl (receptor tyrosine kinase) signaling [98]. Gas6 is a gamma-carboxylglutamic acid (Gla) domain-comprehending protein thought to be involved in the stimulation of cell proliferation. Treatment with VKAs in a preclinical model of pancreatic cancer inhibits the growth of the disease at both its primary and metastatic locations [98]. Inhibition of Gas 6-mediated activation of the Axl receptor tyrosine kinase on cancer cells constitutes the molecular mechanism underlying the antitumor activity, partially unrelated to its impact on coagulation [98].

### Heparin Anticancer Effect

Heparin, a heterogeneous blend of glycosaminoglycans, has potent anticoagulant properties. It is extensively used, with its derivatives, as an anticoagulant to avert VTE. Fortuitously, during the treatment of cancer patients at risk, it has been discovered that heparin and similar medications have anticancer properties [96]. Heparin and its derivatives impact the growth, attachment, formation of new blood vessels, movement, and infiltration of cancer cells through different mechanisms. The primary mechanisms include the suppression of heparanase, angiogenesis, P-/L-selectin, and CXCL12-CXCR4 axis disruption [97,103,104]. These additional biological activities might contribute to the observed anticancer effects. In vitro studies suggest that heparin and derivatives inhibit epithelial cancer growth, migration, and invasion [105-107]. Pre-treatment of experimental lung metastasis models with LMWHs before intravenous inoculation of cancer cells consistently inhibits metastasis development [104]. Conversely, most research studies fail to demonstrate antitumor effects when employing animal models with pre-existing malignancies [104].

Research has shown that LMWH inhibits the growth of different cancer cell lines, such as melanoma, breast, and colon cancer [108,109]. Camacho-Alonso *et al.* found that low-molecular-weight heparin reduces oral cavity squamous cell cancer (OCSCC) proliferation [110]. In a synergistic effect with cisplatin, LMWH's antiangiogenic action inhibits thrombin synthesis, tissue factor expression, and fibrin creation, preventing tumor cell proliferation. In the oral cavity, squamous cell and lung adenocarcinoma, enoxaparin inhibits PI3k/Akt and mitogen-activated protein kinase/Extracellular signal-regulated kinase (MAPK/ERK) signaling pathways to diminish tumor growth and migration [105]. The primary function of the PI3K-AKT signaling pathway is cellular apoptosis inhibition while simultaneously

stimulating cell proliferation and growth (i.e., controlling the cell cycle).

In addition, enoxaparin suppressed the growth and movement of A549 cells [105]. Enoxaparin caused a decrease in the activity of MAPK and PI3K, resulting in a reduction in the production of matrix-metalloproteinase 2 (MMP-2) and the inhibition of A549 cell migration. The MMP-2 controls chemokine monocyte-chemotactic protein 3 processing, generating a chemokine receptor antagonist [111]. Furthermore, enoxaparin enhanced the effectiveness of doxorubicin by promoting apoptosis without any detectable impact on cell-cycle advancement. The research concluded that enoxaparin's ability to prevent cancer in A549 cells was achieved by disrupting two primary PAR-1 downstream signaling pathways, namely, MAPK/ERK and PI3K/Akt. This disruption subsequently hinders cell proliferation and migration [105]. Hence, enoxaparin shows potential as a supplementary treatment to conventional lung cancer chemotherapy and justifies further research.

In patients without malignancy, anticoagulant therapy with LMWHs or VKAs has been effective in preventing recurrent VTE [112]. Research has demonstrated that LMWH treatment is more effective than VKA treatment for reducing recurrent VTE rates in cancer patients. Self-administered LMWHs are unpopular with patients who would rather receive the medication orally, as they necessitate tiresome daily subcutaneous injections. Oral VKAs possess a limited therapeutic window and are vulnerable to numerous drug and dietary interactions [113]. Moreover, regular more frequent monitoring of the anticoagulant effect is necessary [114].

### DOAC Anticancer

DOACs are a newly developed category of oral anticoagulants. They accomplish their action by directly binding to and impeding the thrombin activity or factor Xa (i.e., apixaban, rivaroxaban, and edoxaban). Furthermore, the activated factors X and thrombin initiate the coagulation cascade and stimulate the expression of protease-activated receptors on cancerous and healthy cells [115]. In addition, factor Xa and thrombin activate the intracellular signaling pathways (Ras, PI3K, and mTor) that regulate cancer cell adhesion, migration, and patient survival [115]. Moreover, by forming fibrin/platelet-rich aggregates that encircle circulating tumor cells, coagulation can indirectly aid in widespread metastasis [116], protecting against natural killer-cell-mediated assaults and shear stress. Thrombin triggers tumor cell adhesion to endothelial cells, subendothelial matrix protein, and platelets, promoting tumor development and angiogenesis [115]. Circulating active factor X may overexpress sticky receptors in endothelial cells, promoting the spread of cancer [117]. Hence, DOAC agents that prevent factor X activation may slow this mechanism, limiting tumor survival and metastasis.

Dabigatran administration did not affect OCSCC migration [97]. However, breast cancer-type cells tested with dabigatran showed decreased cell viability [118,119]. Moreover,

oral dabigatran lowers breast cancer cell invasiveness in vitro and mouse tumor development and metastasis [120]. In breast and pancreatic cancer animal models, dabigatran synergistically inhibits tumor development and progression with chemotherapeutic treatments [120,121], which was not noticed in OCSCC [97]. Rivaroxaban, apixaban, and edoxaban inhibit H400 and H357 cancer cell proliferation at various doses. Different mouse model studies indicated no antitumorogenic effects from rivaroxaban [119,122,123]. A mouse-modeled study showed that high-dose apixaban exhibited widespread growth attenuation in colon, prostate, and ovary cancer cell growth [124]. Besides, apixaban reduces ovary and large bowel cancer migration in high-dose therapy [125]. In contrast, rivaroxaban did not impact migration, while low-dose apixaban sped wound closure and high-dose edoxaban at 6–9 h; however, this effect had an insignificant impact after 12 h [97].

### ANTICOAGULATION IN AMBULATORY AND HOSPITALIZED CANCER PATIENTS

Researchers have shown that VTE prophylaxis effectively lowers the likelihood of VTE, although it can cause serious bleeding [126-128]. Nevertheless, the bulk of these trials was conducted previously and mostly focused on radiologic endpoints rather than clinical ones. The presence of these constraints has led to a reassessment of the universal use of thromboprophylaxis in hospitalized patients. This reappraisal is very pertinent to patients receiving medical oncology treatment while hospitalized since no studies have been undertaken to assess the primary VTE prophylaxis effectiveness in medically sick cancer patients. In addition, only a few participants in significant medical prophylaxis trials involved cancer patients [15]. Therefore, there is just a small amount of data to support the use of VTE prevention in hospitalized medical oncology patients.

Several VTE RAMs have been created for medically unwell or undergoing surgery in hospitalized patients [129]. While some of these RAMs have been confirmed in separate groups of patients, it is not yet appropriate to use these models to evaluate the risk in cancer patients. Every RAM considers all types of cancer to have an equal risk of VTE. Furthermore, none of the models included any additional well-established risk factors for cancer-related VTE. None of the RAMs underwent development or validation in cancer patient populations. Hence, it was suggested that all medical and surgical oncology hospitalized patients should be given thromboprophylaxis per the criteria set by the National Comprehensive Cancer Network (NCCN) [130,131].

The American Society of Clinical Oncology (ASCO) recommendations advise the regular use of thromboprophylaxis in all hospitalized patients, except those treated just for a minor operation or chemotherapy [132]. Future research should prioritize showing the effectiveness of VTE prevention in hospitalized oncology patients and creating and verifying cancer-specific VTE RAMs.

The problems that the cancer patients had with VTE prevention were carefully investigated. A prospective study including

2373 cancer surgery patients found that 2.1% of patients had symptomatic VTE throughout a 30–65 days. The average duration until the occurrence of VTE was 17 days. More than 40% of the occurrences occurred more than 21 days after the procedure. The percentage of patients who got thromboprophylaxis during the hospitalization was above 80%, while 31% had prophylaxis after being discharged, and 23% maintained prophylaxis beyond day 21. Being 60 years of age, having a history of VTE, experiencing anesthesia for a minimum of 2 h, having an advanced-stage malignancy, and being confined to bed rest for 4 days are factors that significantly increase the VTE likelihood in individuals with cancer. Among the whole patient population, 41 individuals experienced death after surgical procedures. Out of the total, 19 fatalities (46%) were attributed to VTE, whereas 4 deaths (10%) were due to hemorrhage. Among the four deceased patients, three had previously discontinued the use of VTE prevention [133]. The results have provided evidence for using an initiative-taking strategy for preventing VTE following surgical therapy for cancer patients.

The Enoxacin II trial showed that prolonging the use of enoxaparin to 21 days after surgery, instead of the customary 6–10 days, resulted in a 60% decrease in the VTE relative risk. VTE incidence was 4.8% in the extended-duration enoxaparin group compared to 12% in the standard-duration group. The relative risk reduction was 60% ( $p=0.02$ ) [134]. Nevertheless, out of the 20 events seen in the placebo group, only four were cases of proximal DVT or PE, with just one incident reported. A meta-analysis of seven prospective trials on extended-duration prophylaxis following cancer surgery revealed a 56% reduction in total VTE cases (2.6% vs. 5.6%) and a 54% reduction in proximal DVT cases (1.4% vs. 2.8%). A small decrease in the PE rate was seen in the extended enoxaparin patients' group, with a rate of 0.8% compared to 1.3%. The MB incidence was 1.8% compared to 1.0%, and the rate of all-cause death was 4.2% compared to 3.6% [135,136]. According to these findings, the NCCN and ASCO recommendations suggest that high-risk patients undergoing abdominal-pelvic cancer surgery should get extended-duration prophylaxis [132,137].

Research conducted by Khorana *et al.* observed a group of ambulatory cancer patients who were undergoing chemotherapy. They found that 1.9% of these patients had VTE for 2.4 months, as determined by a median follow-up time [57,138]. Following subsequent randomized thromboprophylaxis studies, there have been notable decreases in VTE, but the actual reductions were not very large [139,140]; however, other studies observed significant decreases in VTE risk in advanced pancreatic cancer [141,142].

In multiple myeloma, VTE risk is nine times greater due to the underlying illness and its treatment [143]. In a clinical study that randomly assigned low-risk myeloma patients to receive either aspirin (ASA) 100 mg daily or ENOX 40 mg daily, it was shown that both treatments were equally effective for preventing VTE. VTE incidence was 2.27% in the ASA group compared to 1.20% in the ENOX group [144]. Khorana *et al.* have devised a risk assessment tool based on evidence to effectively identify cancer

patients who are most likely to benefit from prophylaxis. This method has been verified in many independent investigations [55]. At present, there are ongoing prospective trials that are assessing the effectiveness of DOACs for VTE prevention in high-risk cancer patients.

NCCN and ASCO recommendations advise administering thromboprophylaxis to myeloma patients who are undergoing chemotherapy regimens, including anti-angiogenesis agents. High-risk myeloma patients should have anticoagulant thromboprophylaxis, whereas lower-risk individuals should be given low-dose ASA. The ASCO recommendation suggests that thromboprophylaxis should be considered for additional carefully chosen high-risk individuals. Thromboprophylaxis is not recommended for ambulatory cancer patients and not participating in clinical trials, according to the NCCN guideline [132,137].

## MANAGEMENT OF THROMBOEMBOLISM IN CANCER PATIENTS

### Recommended Initial, Short, and Long-term VTE Therapy in Cancer

VTE treatment can be categorized into three phases: The initial phase (which lasts for the first 5–10 days of therapy), the short-term phase (which spans from month 1 to month 6), and the long-term phase (which lasts for 6 months). Meta-analyses have shown that there is no discernible disparity in the episode of recurrent thrombosis or bleeding between LMWH and unfractionated heparin [145,146]. Unfractionated heparin is recommended for hospitalized patients who need invasive operations or those who have a significant risk of bleeding. LMWH continues to be the recommended treatment for the first and short-term VTE management in cancer. In the comparison of low-molecular-weight heparin versus oral anticoagulant therapy (CLOT) trial, which compared LMWH (dalteparin) with oral anticoagulant therapy (warfarin) for preventing recurrent VTE in cancer, dalteparin was found to reduce the occurrence of recurrent VTE by 50% compared to warfarin (dalteparin vs. warfarin; 9% vs. 17%). In addition, dalteparin had a comparable MB risk (dalteparin vs. warfarin; 6% vs. 4%). The mortality rates were comparable between the two groups, with dalteparin at 39% and warfarin at 41% [112].

Comparison of acute treatments in cancer hemostasis (CATCH) study conducted for 900 patients suffering from active malignancy were randomly assigned to receive either a daily subcutaneous dose of tinzaparin (175 units/kg body weight) or a transition from tinzaparin to warfarin with an international normalized ratio target range of 2–3. Recurrent VTE incidence was quantitatively lower in patients given tinzaparin compared to those who had warfarin (7.2% vs. 10.5%). The incidence of significant bleeding (2.7% for tinzaparin vs. 2.4% for warfarin) and death 34.7% for tinzaparin vs 32.2% for warfarin) were comparable [147]. The duration of these trials was restricted to 6 months.



The DALTECAN trial was conducted to examine the results linked to the extended use of LMWH for treating VTE in cancer. The DALTECAN trial recruited patients with active cancer and new VTE to receive dalteparin for 12 months to verify the effectiveness of long-term LMWH. Out of the 334 patients that were recruited, 185 of them (54.7%) successfully finished 6 months of therapy, while 109 patients (32.2%) completed the full 12 months of treatment. The primary causes for withdrawal were mortality (73 cases, 33.2%), adverse events (60 cases, 26.2%), voluntary withdrawal of permission (42 cases, 18.3%), and 37 patients (11.1%) who had recurrent VTE. The recurrent VTE rate was 8.7% during the initial 6 months and 4.1% between months 7 and 12. Thirty-four patients (10.2%) had significant hemorrhage. The occurrence of significant hemorrhage was 3.6% during the 1<sup>st</sup> month and ranged from 0.8% to 1.8% per month between months 2 and 6, and from 0% to 1.4% per month between months 7 and 12. Within the 12-month trial period, 116 patients, accounting for 33.8% of the participants, succumbed to their conditions. Specifically, 105 patients died because of cancer, two from hemorrhage, and four from PE [148].

A review article by Kahale *et al.* concluded that long-term VTE treatment in cancer, LMWHs in comparison to VKAs might produce a considerable VTE rate decrease. In contrast, DOACs versus LMWH, DOAC are more effective in the reduction of VTE, albeit they might increase the MB risk. Hence, the risks and advantages of the anticoagulant agents to be used must be carefully assessed in long-term anticoagulation [149]. While systematic reviews and recommendations advocate for using LMWH in treating VTE in cancer, a study of the Registro Informatizado de Enfermedad TromboEmbolica indicates that VKAs might potentially be beneficial for cancer patients who have had 6 months of LMWH medication. Out of the 1502 malignancy patients who were treated with LMWH for 6 months, 763 patients chose to remain with LMWH, whereas 739 patients opted to switch to warfarin. The VTE recurrent incidence and serious bleeding events were comparable [150]. An analysis of malignancy patients with VTE found that warfarin treatment had more positive outcomes when compared to LMWH [151]. These trials indicate that VKAs may have comparable efficacy to LMWH in a substantial number of malignancy patients with VTE. Additional investigation is necessary to validate these results.

Extensive randomized clinical studies have shown that DOACs are as efficacious, if not more so, compared to traditional treatment including LMWH followed by VKA. Nevertheless, a limited cohort of cancer patients was included in different trials. Vedovati *et al.* conducted a meta-analysis and observed that recurrent VTE occurred in 3.9% of DOAC-treated patients, compared to 6% of VKA-utilized patients. In addition, severe bleeding occurred in 3.2% of DOAC patients and 4.2% of VKA patients [152]. The data of these trials demonstrate a considerable improvement compared to prior research on cancer-related blood clotting. This could indicate that the patients included in the DOAC studies were not similar to the patients included in the CLOT and CATCH studies [112,147,152-154].

Within the RECOVER investigation, a mere 13% of patients who had active cancer at the beginning of the study had developed metastatic illness. In addition, the overall death rate for all causes was just 15% [153]. Prins *et al.* reported that the proportion of cancer patients at the beginning of the study who had metastatic illness was only 22%, and 30% of them had chemotherapy as a form of treatment. The overall death rate was just 16% [155]. A study by Agnelli *et al.* noted that over one-third of participants had metastatic illness. However, the death rate for cancer patients receiving apixaban was 6%, whereas for those taking warfarin, it was 7.7% [156]. Moreover, there were notable discrepancies in the criteria for inclusion and exclusion across the studies on DOACs in CLOT and CATCH studies.

A total of 200 cancer-related VTE patients received a complete course of rivaroxaban. Symptomatic proximal lower limb DVT, recent or recurrent PE, clinically significant non-MB, MB, leading to rivaroxaban cessation, or death were the key outcomes at 6 months in competing risk analysis. The 6-month new or recurrent VTE cumulative incidence was 4.4%, severe bleeding was 2.2%, and all-cause death was 17.6% in competing risk analysis. In this research, new or recurrent VTE and serious bleeding rates were similar to the EINSTEIN cancer subgroup analysis [154]. A study suggested that Rivaroxaban is safe and effective for cancer-related VTE, compared to LMWH [157].

Another previous research conducted that involved 118 patients with cancer-linked thrombosis who were treated with rivaroxaban saw a non-significant difference in VTE recurrence in cancer and noncancerous patients (3.3% vs. 2.8%, respectively) after an average follow-up period of 1.3 years [155]. Chemotherapy was administered to 90 cancer patients, accounting for 76% of the total. Out of the total number of patients, specifically, 22% of those who had cancer passed away. However, none of the non-malignant patients died. Comparable results were documented in research conducted at the Memorial Sloan Kettering Cancer Center [155]. Despite the promising nature of these findings, the author maintains that it is early to use DOACs as primary agents for treating cancer-related VTE. The Hokusai VTE cancer study and similar ongoing studies will be crucial in validating the findings of previous trials. Therefore, the NCCN and ASCO recommendations advise against DOAC use until more data is available about their effectiveness in individuals with cancer.

The current recommendations from NCCN, ASCO, and the American College of Chest Physicians advise that anticoagulation better be maintained for cancer-associated VTE as long as the cancer is not cured or continuing cancer treatment [15,137,158]. There is insufficient data from randomized studies to determine the optimal duration for anticoagulation therapy in cancer patients. Therefore, the only sources of advice are professional opinion and common sense. Hence, medical practitioners should evaluate these options individually by examining unbiased imaging results for enduring malignancy, tumor markers, and enduring risk factors for VTE, together with the patient's preferences, the likelihood of bleeding associated with anticoagulation, and treatment adherence.

Several risk factors and reasons for recurrent VTE have been found in cancer, including a validated RAM called The Ottawa Score [159]. The cancer duration of anticoagulation based on compression ultrasonography study found that a negative duplex ultrasound after therapy is associated with a significantly decreased recurrent VTE risk. Specifically, the risk was 2.8% for those with a negative ultrasound compared to 21.9% for those without. Furthermore, end-of-therapy duplex tests provide evidence of any remaining illness if the patient has symptoms that might indicate a new blood clotting event. Despite the varied outcomes of validation studies on the Ottawa Score, the authors believed it is vital to consider established evidence-based risk factors when deciding on anticoagulant medication for cancer patients [160,161]. Despite all these recommendations, there are still ambiguities in deciding when to start and when to stop anticoagulation in malignancy patients to prevent this highly prevalence complication. Therefore, further trials are required to establish a plan for cancer patients concerning VTE prevention.

### **VTE Therapy in Thrombocytopenic Cancer Patients**

A  $50 \times 10^9/L$  thrombocyte count is widely recognized as the minimum safe level for therapeutic anticoagulation [132]. According to the International Medical Prevention Registry on VTE VTE prophylaxis registry, individuals with a thrombocyte count below  $50 \times 10^9/L$  had a threefold increased risk of developing bleeding [162]. Preliminary studies have shown that individuals with thrombocyte counts below  $50 \times 10^9/L$  may benefit from lower doses of anticoagulation [163,164]. The International Society on Thrombosis and Hemostasis has released a recommendation sheet that provides a logical strategy for managing patients with both thrombocytopenia and VTE based on the currently available evidence [165]. Additional research is necessary to assess the effectiveness and safety of conventional and reduced-dose anticoagulation treatments at various thrombocyte counts in cancer patients who develop VTE.

## **RECURRENT VTE MANAGEMENT IN CANCER**

### **Medical Therapy**

It is crucial to empirically confirm the presence of VTE recurrence because symptoms may be resembled by infections (e.g., pneumonia), cardiac and pulmonary failure, post-thrombotic syndrome, or hepatic or renal disease. The cause or causes of a recurrent VTE has/have to be determined, and an alternative course of treatment should be initiated upon confirmation of the recurrence of the VTE. Alternate treatment options include modifying the dosage or administration schedule, transitioning to fondaparinux (chemically related to LMWHs), which possesses a prolonged elimination half-life, or utilizing an LMWH or unfractionated heparin.

Subtherapeutic anticoagulation resulting from non-compliance with treatment, hemorrhage, or thrombocytopenia are prevalent factors contributing to recurrent VTE. In such situations, it is

critical to implement adherence-enhancing strategies (e.g., closer monitoring, perioperative bridging anticoagulation, and alternative anticoagulant regimens). Trousseau syndrome associated with progressive cancer or inadequately managed neoplastic disorders (e.g., persistent erythrocytosis, polycythemia vera) may give rise to intrinsic or endogenous therapeutic resistance. Trousseau syndrome is frequently associated with recurrent or spontaneous deep venous thromboses or migratory superficial in occult or newly diagnosed visceral malignant disease. However, the term is occasionally applied to describe hypercoagulability that is linked to any malignant condition [166].

Heparin therapy and active management of the underlying cancer are critical in preventing recurrent thromboembolism in Trousseau syndrome patients. Effective management of erythrocytosis is vital for the efficacy of anticoagulant regimens in patients with polycythemia rubra vera. In cancer patients, heparin-induced thrombocytopenia may occasionally result in recurrent VTE, requiring the standard therapy for heparin-induced thrombocytopenia. Therapeutic resistance can be induced by extrinsic factors such as vascular stasis caused by compression due to tumor or nodal masses or thrombosis precipitated by turbulence and obstruction of blood flow caused by CVCs or VCFs. In these situations, it is critical to eliminate the source of the stasis.

As a successful strategy for anticoagulation management, LMWH dose escalation has been demonstrated effective in VTE recurrence prevention [167]. Approximately 73% of the 212 cancer patients with recurrent VTE in an international registry had metastatic cancer during the event, and 70% were taking LMWH. Approximately 70% of those with breakthrough thrombosis were receiving a therapeutic or more than therapeutic dose. Following this, 24% of the participants shifted to a different medication, while 31% were prescribed an increased therapeutic dose and 33% continued on the same dosage. Approximately 11% experienced a recurrence of a VTE within 3 months of follow-up, 8% developed severe hemorrhage, and 27% passed away. Recurrent VTE was a less frequent complication of LMWH compared to VKA [168]. This study highlighted the difficulties and provided support for LMWH use in managing cancer patients with recurrent VTE. However, new prospective studies are required to clarify those issues.

### **Interventional (Mechanical) Therapy**

The vena cava filter (VCF) is used to prevent thrombus migration beyond the filter that is usually inserted in the abdominal inferior vena cava. The only indication for a VCF in cancer subjects is the presence of an acute DVT and/or PE, together with a contraindication for anticoagulation [169,170]. Given that the likelihood of a thrombotic recurrence occurs during the 1<sup>st</sup> month of cancer diagnosis, health-care professionals will generally deem it suitable to employ a VCF if a patient must stop taking anticoagulant medication during this period. In cases where a patient has experienced a thrombotic event over a month ago,

the use of VCFs is considered individually. Factors such as the location and size of the thrombus, the anticoagulation treatment duration, the expected duration of time without anticoagulation, and the patient's other existing health conditions should be considered. Utilizing a retrievable filter is advisable since it maintains the possibility of subsequent extraction. It is essential to establish a methodical monitoring procedure to guarantee the retrieval of filters whenever they become unnecessary [171].

### COMPARISON BETWEEN THE EFFECTIVENESS OF AVAILABLE ANTICOAGULANTS

Cancer-associated VTE has been significantly more effectively treated in recent years. In *individuals* with cancer, DOACs have become the VTE standard therapy. RCTs comparing the DOACs and LMWHs' safety and efficacy supported their application [172-175]. Despite the demonstrated DOACs' efficacy in reducing the recurrence of thrombosis rate among cancer patients, the potential for hemorrhage remains a significant concern, particularly for individuals with GI malignancies. Hokusai VTE cancer trial reported that GI cancer patients who received edoxaban treatment experienced severe bleeding events at a substantially significantly higher rate (13.2% vs. 2.4%) than those who received dalteparin [172]. With esophageal or gastroesophageal malignancies, patients who were administered rivaroxaban in the SELECT-D study exhibited a significantly higher hemorrhage incidence (36% vs. 5%) compared to those who were treated with dalteparin. As a result, patient recruitment for the ongoing trial involving this form of tumor was halted [173]. In contrast, the Apixaban and dalteparin in active malignancy-associated VTE and Caravaggio trials found the bleeding attack incidence did not differ significantly in active malignancy-associated VTE between dalteparin and apixaban participants [174,175], particularly in GI malignancies.

During the early 2000s, research demonstrated that administering a twice-daily oral dose of ximelagatran effectively reduces recurrent VTE [176], averted post-operative VTE, and was a viable immediate treatment option for DVT [177]. However, hepatotoxicity, on the other hand, led to ximelagatran withdrawal [178]. It was reported that DOACs have more significant predictable pharmacokinetic and pharmacodynamic properties than VKAs [179,180]. Randomized clinical studies reported that other DOACs (rivaroxaban, edoxaban, etexilate, apixaban, and dabigatran) are the best alternatives to VKA in patients without malignancy [156,181]. These alternatives have comparable or superior antithrombotic efficacy. Rivaroxaban [173] and edoxaban [172] have proven comparable efficacy to dalteparin in cancer patients concerning the composite outcome of significant hemorrhage or recurrent VTE. At present, edoxaban or rivaroxaban is the DOAC of choice for preventing recurrent VTE in cancer-affected persons with a significant risk of hemorrhage [182,183].

Patients diagnosed with GI cancer have an elevated susceptibility to VTE. Based on the results of randomized clinical trials involving cancer-associated VTE, DOACs administered

to patients with GI cancer exhibited comparable or superior efficacy but a heterogeneous safety profile [184]. The available data suggest that utilizing DOACs to treat GI cancer-associated thrombosis may increase the clinically relevant non-MB (CRNMB) risk. There were no considerable differences in the MB risks; however, it has been observed recently that DOACs' efficacy in VTE recurrence prevention is comparable to LMWH's efficacy [185].

DOACs have emerged as a viable substitute for LMWHs in managing cancer-induced thrombosis. Although DOACs were found to be comparable to LMWHs in preventing recurrent VTE among genitourinary and GI tract malignancies, subgroup analyses revealed that specific DOACs posed greater risks of hemorrhage than LMWHs [186,187]. However, a systematic review with meta-analysis of DOAC use in acute VTE treatment in GI cancers is required. Severe hemorrhage or recurrent VTE major differences between DOACs and LMWH participants were not noted. Furthermore, comparing luminal and non-luminal GI malignancies revealed comparable levels of significant hemorrhage. On the contrary, the DOAC-treated participants exhibited an increased incidence of CRNMB compared to the LMWH-treated participants.

A study reported that rivaroxaban treatment in atrial fibrillation has a lower rate of causing GI bleeding than warfarin-managed patients [188]. Furthermore, CRNMB and MB in the GI were substantially less within LMWH than among the rivaroxaban-treated group [173]. Cancer patients who received edoxaban in the Hokusai VTE cancer trial experienced a greater incidence of significant bleeding, but not CRNMB, compared to those who received dalteparin. Also, they observed an increased incidence of GI hemorrhage among GI malignancy patients [172]. In contrast, severe GI hemorrhage risk did not differ significantly between cancer apixaban-treated and LMWH-treated patients [174,175]. Intriguingly, DOAC type was used to treat acute VTE, and bleeding risk analysis did not identify any significant differences between the subgroups treated with apixaban and rivaroxaban in terms of severe bleeding. This finding may advocate that GI cancer therapy of associated VTEs by DOACs is not the only hemorrhage risk factor; however, the CRNMB of rivaroxaban patients was greater in this meta-analysis than LMWH patients.

DOAC users experienced comparable severe bleeding events [189,190] as those taking LMWH despite higher CRNMB [187]. While the present meta-analysis did not identify any statistically significant disparity in the MB rates between patients who used DOACs or LMWHs, a discernible pattern indicated an elevated incidence of MB within the DOAC-treated group. In addition, the effectiveness of DOACs in VTEs' recurrence prevention was comparable to LMWH. Hence, DOACs ought to be regarded as a viable substitute for LMWH in acute VTE management, as there is no statistically significant disparity in severe hemorrhage among patients with GI malignancies. DOACs relate to an increased CRNMB; this should be fully considered when deciding whether to prescribe them to GI cancer patients. Before beginning treatment, the risk of hemorrhaging should be exposed and discussed clearly with the patient.

**Table 2: Comparison between heparin, VKA, and DOAC medications in cancer patients**

Variable	Heparins	VKAs	DOACs
Indication	Therapy and prophylaxis	Prophylaxis	Prophylaxis
Administration route	S/C or IV	Oral	Oral
Frequency	> Once/day	Once daily	Once daily
Bleeding risk	Yes, but it is much less	Yes/common	Yes, but less, usually GI cancer
Bleeding	Easily controllable/compression and protamin sulfate	Needs admission usually, Vitamin K, and blood transfusion	Only stoppage of the drug is usually enough; rarely, an antidote or blood transfusion is needed.
Follow up	Frequent	More frequent to check INR	No need for frequent clinic visits
Side effect	Thrombocytopenia, osteoporosis, etc.	Bleeding, diarrhea, blurred vision, etc	Bleeding usually minor
VTE recurrence	Can occur (rarely)	May occur	Far less likely to reoccur with less Hge risk
Usage in breastfeeding	Can be used throughout the whole pregnancy	Not advised, but warfarin can be used	Not indicated
Bridging	Not needed	Required	Not needed
Safety	Safe, but the side effects and route of administration are the problems	Save but bleeding risk	More safer
Anticancer	impact the growth, attachment, new blood vessel formation, movement, and infiltration and migration of cancer cells	antiproliferative properties, inhibit tumor migration, and decrease cancer risk (lung, breast)	regulate cancer cell adhesion, migration, and inhibition of tumor development

Hge: Hemorrhage, DOAC: Direct oral anticoagulants, VKAs: Vitamin K antagonists, SC: Subcutaneous, IV: Intravenous, GI: Gastrointestinal

A meta-analysis was conducted to compare recurrent VTE risk and overall hemorrhage in cancer-associated thrombosis managed with DAOCs versus LMWH in three observational studies [191]. Another meta-analysis of 11 studies involving GI cancer patients was conducted [185]. The visual examination of forest sites was employed to assess the consistency of these studies; the presence of low I2 values indicated the absence or minimal heterogeneity. Rungjirajitranon *et al.* claimed the inconsistencies are due to the inadequate number of occurrences and patients enrolled, which may hinder the capability to identify statistically significant variations in certain outcome determinations, such as VTE recurrence rate [185]. In addition, crucial baseline characteristics of the patient that could potentially impact the likelihood of thrombosis were not captured, including patient status (i.e., managed as inpatient or outpatient), sex, age, and cancer treatment.

Furthermore, there was variation in the definitions of primary outcomes across the included studies. Fourthly, recurrent thrombosis was the primary outcome in only three studies. Moreover, assessing heterogeneity through analytical means was not feasible due to the meta-analysis restricted sample size. Finally, the restricted quantity of studies hindered the assessment of publication bias. Therefore, further prospective studies and meta-analyses based on new data are required to evaluate the best anticoagulant that has a preventive VTE effect and anticancer action in cancerous patients. Table 2 summarizes the comparative differences and side effects between DOAC, heparins, and VKAs in cancer patients. Table 2 compares between the effectiveness of heparin, VKA, and DOACs medications.

## CONCLUSION

VTE occurs frequently as a complication in cancer patients who are actively ill. Over the past two decades, observational studies and randomized clinical trials have made significant contributions to our knowledge of the pathogenesis and treatment of VTE. Nonetheless, there are still unanswered inquiries that require attention. These include the most effective strategy for primary prophylaxis in inpatient and ambulatory patients like medical oncology, the management of cancer-associated VTE in populations with standard and high bleeding risks (e.g., appropriate therapy duration, anticoagulant regimen), and the function of DOACs in localized and metastasized cancers. Fortunately, clinical research is actively focused on cancer-associated thrombosis; thus, answers to these crucial concerns should be forthcoming.

Anticoagulation is crucial at the time of diagnosis, after cancer surgery, and during chemotherapy for varied reasons, including the prevention of VTE and its antitumor effects. Nevertheless, the potential for bleeding, tumor dissemination, and VTE recurrence should be carefully considered concerning their advantages. While heparin preparations are considered the safest anticoagulants, their delivery methods may be uncomfortable. VKAs and DOACs are superior due to their oral administration route. Unfortunately, VKAs need regular INR monitoring and have the potential to induce significant and protracted bleeding as compared to DOACs.

## AUTHORS' CONTRIBUTIONS

All authors have made a significant contribution to the work reported, whether in conception, study design, implementation,

data collection, data analysis, and interpretation, or all of these areas, they also participated in drafting, revising, or critically reviewing the article and gave final approval to publish the version.

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*Funding: None; Conflicts of Interest: None Stated.*

**How to cite this article:** Habas E, Habas A, Rayani A, *et al.* Updated review on malignancy-associated venous thromboembolism: Pathogenesis and comparison between various therapeutic modalities. *Yemen J Med.* 2024;3(1):4-20.