

# Direct Oral Anticoagulants in the Management of Cancer-Associated Venous Thromboembolism: A Comprehensive Review

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**Abstract** Venous thromboembolism (VTE) is reportedly the second common cause of death among cancer patients. Management of VTE with low molecular weight heparins (LMWH) and Vitamin K antagonists (VKA) is associated with significant clinical challenges that led to the emergence of direct oral anticoagulants (DOAC) as an alternative for the management of cancer-associated thrombosis (CAT). The objective of this review is to provide an updated review of the completed and upcoming randomized controlled clinical trials (RCT) comparing the safety and efficacy of DOAC versus LMWH in the management of CAT in adults. A comprehensive literature survey was conducted till 7th January 2021 to review the completed randomized controlled clinical trials (RCT) comparing the safety and efficacy of DOAC versus LMWH in the management of CAT in adults. In order to search for upcoming trials, the Cochrane library and clinicaltrials.org databases were surveyed until the same period. The author found four completed RCT of DOAC in the management of CAT. Apart from these, there were another four RCT that are either ongoing or are yet to publish data. DOAC were reported to be noninferior to LMWH in the treatment of cancer-associated thrombosis in cancer patients with low bleeding risk and without gastrointestinal or gastrourinary cancers. Among patients with gastrointestinal or gastrourinary cancers and VTE, LMWH are preferred.

**Keywords** Venous Thromboembolism, Cancer, DOAC

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## 1. Introduction

Venous thromboembolism (VTE) is a major cause of morbidity and mortality in patients with cancer [1]. The rate of occurrence of VTE in cancer patients is observed to be significantly higher than in the general population with an annual incidence of around 1 in 200 cases [2,3]. VTE is reported to be the second most common cause of death among cancer patients after cancer itself. Moreover, the therapies related to cancer, such as chemotherapy, radiation therapy, hormonal therapy, targeted therapy, and surgery, are further reported to increase the risk of VTE events [4]. VTE is often considered to be a negative predictor of survival in patients with cancer. Patients with cancer and VTE often require more hospitalizations, have a higher rate of metastatic disease, and their overall survival rate is worse compared to those without VTE [5].

Various mechanisms have been implicated in the pathophysiology of the development of VTE in different types of cancers [6]. The thromboembolic events in cancer can be explained by three basic mechanisms, namely, cell-mediated, through leucocytosis and thrombocytosis,

microparticle-based, through the expression of tissue factor and/or phospholipid, and humoral, via enhanced expression of circulating inflammatory markers. Along with these mechanisms, other associated factors such as immobility of the patient, frequent hospitalizations, central venous catheters, surgery, radiation therapy, and vascular toxicity of chemotherapeutic agents together contribute towards the development of cancer-associated thrombosis. All these events leading to VTE were first schematically described by Rudolf Virchow in the year 1856 and are popularly known as “Virchow’s triad.” It had classified all these events into the three major components that lead to cancer-associated thrombosis, namely, venous stasis, endothelial injury, and hypercoagulability [7].

The choice of anticoagulants has been a major challenge in cancer patients as they present with increased episodes of VTE recurrence and bleeding during the course of VTE management [8,9]. The primary goals of VTE therapy include stabilization of the clot, prevention of embolization, avoidance of the recurrence of VTE, and prevention of future complications. However, a host of factors can pose major challenges in the management of VTE in cancer. The commonly used anticoagulants, such as low-molecular-weight heparins (LMWH), direct oral anticoagulants (DOAC), and vitamin K antagonists (VKA), have certain advantages and significant disadvantages. Daily injections and platelet count monitoring in the case of LMWH therapy or regular monitoring of the International normalized ratio (INR) and subsequent dose adjustments in VKA therapy hamper the quality of life of the patients. The gastrointestinal abnormalities associated with chemotherapy or surgery make the management of VTE with VKA difficult in these patients. Pharmacokinetics of VKA and their drug interactions with other medications can affect their anticoagulation properties. Studies reported that cancer patients with VTE treated with conventional anticoagulants (Unfractionated heparin or LMWH) have higher rates of both recurrent VTE (3 times higher) and major bleeding complications (6.5 times higher) than do patients without underlying malignancy [10]. This emphasizes the need to cautiously initiate anticoagulation treatment and to closely monitor patients to achieve a balance between the hemorrhagic and thrombotic risks in this challenging patient population.

However, irrespective of the choice of drug, anticoagulation therapy remains a major challenge for cancer patients. Extended anticoagulation administration beyond the initial period of 6 months of treatment of VTE in these patients is an important consideration. The present study was conducted to provide an updated review of the completed and upcoming randomized clinical trials on the use of DOAC in the management of cancer-associated thrombosis to evaluate the efficacy and safety of DOAC compared with LMWH in this patient population.

## 2. Methods

A comprehensive literature survey was conducted in PubMed till 7<sup>th</sup> January 2021 for the relevant publications of all the completed Randomized controlled trials (RCT) reporting DOAC in the management of cancer-associated thrombosis in adults. Inclusion criteria were: RCT with study population consisting of adult (age >18 years) patients with active malignancy and cancer-associated thrombosis with the intervention consisting of DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) compared to LMWH.

To identify the current treatment guidelines for the management of VTE in cancer, the recommendations by the American Society of Clinical Oncology (ASCO), the American College of Chest Physicians (ACCP), the European Society of Medical Oncology (ESMO), The International Society on Thrombosis and Haemostasis (ISTH), and the International Initiative on Thrombosis and Cancer (ITAC) were also referred. In order to search for the upcoming trials, the Cochrane library and clinicaltrials.org databases were surveyed till the same period.

The keywords used in the literature search were “cancer and VTE,” “DOAC and cancer,” “Anticoagulation and cancer.”

## 3. Results

The database search identified 464 citations. 460 citations were excluded for not meeting the inclusion criteria and for duplications. There were four multicentered completed RCT comparing DOAC to LMWH in the management of cancer-associated thrombosis conducted on a well-defined patient population (Table 1). All these trials have their data published in peer-reviewed journals reporting a detailed account of all the study endpoints along with the adverse outcomes. Treatment duration was at least 6 months in all trials [11-14].

Furthermore, the Hokusai VTE trial included data from 12 months follow-up, and patients in the SELECT-D trial were also eligible for randomization to a further 6 months of rivaroxaban or placebo. In the four completed RCT, the LMWH used was dalteparin.

All the reviewed studies reported that DOAC were noninferior to LMWH for the treatment of cancer-associated thrombosis. DOAC were reported to have a significantly lower risk of VTE recurrence compared with LMWH. However, the risk of clinically relevant nonmajor bleeding (CRNMB) was significantly higher with DOAC than with LMWH. Gastrointestinal and gastrourinary cancers were associated with a higher risk of CRNMB.

There are several more RCT that are either ongoing or are yet to publish data. The major concerns for DOAC management included thrombocytopenia and reduced renal clearance in CKD patients.

## 4. Discussion

The landmark CLOT [15] study (Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) had randomized the comparison of LMWH versus VKA therapy for the prevention of recurrent VTE in patients with cancer. The study reported the superiority of dalteparin over warfarin (recurrent VTE 8% vs. 16%;  $p = 0.002$ ) without increasing major bleeding risks [15]. The outcome of the CLOT trial, along with other studies [16] confirms the efficacy of LMWH over VKA with comparable safety. This made LMWH the recommended drug of choice for the treatment of VTE in major clinical practice guidelines, including the American College of Chest Physicians (ACCP) [17], American Society of Clinical Oncology (ASCO) [18], and the European Society of Medical Oncology (ESMO) [19]. However, the burden of regular injections, the high cost of LMWH, and the long-term risks resulted in recent trials comparing DOAC with LMWH for the management of cancer-associated thromboembolism.

Some DOAC agents that are already in use in the management of cancer-associated thrombosis include dabigatran, rivaroxaban, apixaban, and edoxaban [16]. Over the past few years, the use of DOAC has revolutionized the treatment of venous thromboembolism. Several clinical trials and post-marketing data have served to recommend DOAC as the preferred therapy over VKA for the treatment of VTE in patients without cancer [20-22]

Until recent years, studies comparing efficacies of DOAC with warfarin were conducted in the general population with thromboembolic events, and secondary sub-group analyses validated and reported the results in cancer patients out of the recruited subjects. The EINSTEIN trial [20] that compared rivaroxaban with warfarin and the RE-COVER trial [21] that compared

dabigatran with warfarin did not report any significant difference in recurrence or bleeding events. The efficacy and safety of DOAC compared to LMWH in well-defined cohorts of cancer with VTE are being lately studied through randomized controlled trials. Though limited in number, some of these trials are already completed, while some are still ongoing.

### 4.1. Hokusai VTE Trial

The efficacy of edoxaban was reported through the Hokusai [11] VTE Cancer trial. The study included 1050 cancer patients with acute symptomatic or incidental PE or proximal VTE. Patients were randomized to receive either therapeutic LMWH for five days, followed by edoxaban 60 mg daily or dalteparin 200 IU/kg daily for one month, followed by a daily dose of 150 IU/kg. The duration of treatment was for 6–12 months.

The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration. The main types of cancers included in the edoxaban arm vs dalteparin arm were colorectal (15.9% vs 15.1%), lung (14.8% vs 14.3%), genitourinary (12.5% vs 13.5%), breast (12.3% vs 11.5%), pancreatic or hepatobiliary (9.4% vs 7.6%), gynaecological (9% vs 12%), upper gastrointestinal (6.3% vs 4%), other cancers (9.2% vs 11.5%), and haematological malignancies (10.7% vs 10.5%).

Edoxaban was reported to be noninferior to dalteparin (HR 0.97,  $p = 0.006$  for noninferiority). CRNMB was reported in 12.3% of patients in the edoxaban group vs 8.2% of patients in the dalteparin group (HR 1.55, 95% CI, 1.05-2.28). Also, the rates of recurrent VTE in the edoxaban group did not differ significantly from those in the dalteparin group (7.9% in the edoxaban arm versus 11.3% in the dalteparin arm,  $p=0.09$ ) [11].

**Table 1.** List of completed clinical trials included in this review

Clinical trial	Sample size	Study design	Follow up	Primary outcome	Study treatments	
					DOAC	Comparator
Hokusai [11]	1,046	RCT (Open-label) (noninferiority)	12 months	composite of recurrent VTE or major bleeding	Edoxaban	Dalteparin
SELECT-D [14]	406	RCT (Open-label) (pilot trial)	6 months	VTE recurrence	Rivaroxaban	Dalteparin
ADAM VTE [12]	300	RCT (Open-label) (superiority)	6 months	Major bleeding	Apixaban	Dalteparin
Caravaggio [13]	1,155	RCT (Open-label) (noninferiority)	6 months	Efficacy: VTE recurrence Safety: Major bleeding	Apixaban	Dalteparin

RCT (randomized clinical trial); VTE (venous thromboembolism)

#### 4.2. ADAM VTE Trial

The ADAM VTE trial [12] compared the efficacy of apixaban with respect to dalteparin, assessing the risk of major bleeding as the primary endpoint. Three hundred patients with active cancer and acute VTE were randomized to receive either apixaban 10mg twice daily for seven days, followed by 5mg twice daily for six months or subcutaneous dalteparin 200 IU/kg for one month followed by 150 IU/kg once daily. The duration of treatment was for six months.

The main types of cancers included in the apixaban arm vs dalteparin arm were colorectal (12.2% vs 19.6%), ears, nose, and throat (2.05% vs 0.7%), genitourinary (8.7% vs 9.3%), gynecologic (9.5% vs 10.1%), lung (21.8% vs 12.8%), melanoma (0.0% vs 2.7%), neuroendocrine (1.4% vs 2.0%), pancreatic/hepatobiliary (15.6% vs 16.2%), sarcoma (2.0% vs 0.7%), thyroid (0% vs 0.7%), upper gastrointestinal (4.8% vs 2.7%), other cancers (0.0% vs 0.7%), and hematologic malignancies (2.9% vs 2.6%).

None of the patients (0.0%) receiving apixaban had shown major bleeding incidence in comparison to 1.4% of patients receiving dalteparin ( $p=0.138$ ; HR inestimable for 0 bleeding events in the apixaban group). As for the secondary endpoint considerations, recurrent VTE was reported in 0.7% of the apixaban group in comparison to 6.3% of the dalteparin group (HR 0.099, 95% CI, 0.013-0.780,  $p = 0.0281$ ). CRNMB was reported in 6.2% of patients in the apixaban group vs 4.2% patients in the dalteparin group. Hence, this trial reported that oral apixaban was associated with low major bleeding and VTE recurrence rates when used for the treatment of VTE in cancer patients [12].

#### 4.3. CARAVAGGIO Trial

The efficacy of apixaban with dalteparin as the comparator was also studied in the CARAVAGGIO [13] trial. However, the prevention of recurrent VTE without increasing the risk of major bleeding was the primary outcome consideration in this trial. 1,155 Cancer patients with symptomatic or incidental acute proximal DVT or PE were randomized either to receive oral apixaban, 10 mg twice daily for the first seven days, followed by 5 mg twice daily or subcutaneous dalteparin (200 IU/kg once daily for the first month, followed by 150 IU/kg once daily). The duration of the treatments was for six months.

The main types of cancers included in the apixaban arm vs dalteparin arm were colorectal (21% vs 19.5%), lung (18.2% vs 16.4%), breast (13.7% vs 13.1%), genitourinary (11.5% vs 12.6%), gynaecological (10.4% vs 10.2%), pancreatic or hepatobiliary (7.6% vs 7.4%), upper gastrointestinal (4.0% vs 5.4%), head and neck (2.4% vs 1.4%), bone and soft tissue (1.9% vs 1.2%), skin (0.7% vs 1.2%), other cancers (2.8% vs 2.6%), and haematological malignancies (5.7% vs 9.0%).

On primary endpoint analysis, it was observed that 5.6%

of patients in the apixaban group had recurrent VTE events compared to 7.9% of patients in the dalteparin group (HR, 0.63; 95% CI, 0.37 to 1.07;  $p<0.001$  for noninferiority). Major bleeding was observed in 3.8% patients in the apixaban group compared to 4.0% in the dalteparin group (hazard ratio, 0.82; 95% CI, 0.40 to 1.69;  $p = 0.60$ ). CRNMB was reported in 9% of patients in the apixaban group vs 6% of patients in the dalteparin group (HR 1.42, 95% CI, 0.88-2.3). Hence, this had reported evidenced-based conclusion of oral apixaban being noninferior to subcutaneous dalteparin for the treatment of cancer-associated thrombosis without increasing the risk of major bleeding [13].

The safety and efficacy of rivaroxaban for the prevention and treatment of cancer-associated thrombosis are currently being studied globally under the CALLISTO international clinical research program. The program includes multiple RCT and non-interventional studies along with guidance on drug-drug interactions. The program involves more than 3000 patients worldwide, and besides its primary outcome considerations, it also evaluates treatment satisfaction and adherence with rivaroxaban and insight into real-world management and patterns of anticoagulation use.

#### 4.4. SELECT-D Trial

One of the completed trials under the CALLISTO program was the SELECT-D [14] trial. The study had randomized 406 cancer patients with acute symptomatic or incidental PE or symptomatic proximal DVT to either rivaroxaban (15 mg twice daily for 3 weeks, then 20mg once daily) or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily). The treatment durations were six months and five months, respectively.

The primary outcome in the SELECT-D trial was VTE recurrence, and the secondary outcome was major bleeding and CRNMB. The main types of cancers included in the rivaroxaban arm vs dalteparin arm were bladder (5.0% vs 2.0%), brain (1.0% of each arm), breast (10% of each arm), unknown primary (1.0% vs 2.0%), chronic lymphoid leukemia (1% of each arm), colorectal (27% vs 23%), gallbladder (1.0% of each arm), gastrointestinal (2.0% vs 3.0%), gynecological (3.0% of each arm), kidney (1.0% vs 3.0%), lung (11% vs 12%), lymphoma (5.0% vs 6.0%), multiple myeloma (1.0% vs 2.0%), esophageal and gastroesophageal (5.0% vs 9.0%), ovarian (6.0% vs 9.0%), pancreatic (9.0% vs 5.0%), prostate (7.0% vs 4.0%), sarcoma (1.0% vs 0.0%), other cancers (3.0% in each arm), and unknown (1.0% vs 2.0%).

The rate of recurrent VTE was observed to be 4% in the rivaroxaban group in comparison to 11% in the dalteparin group (HR, 0.43, 95% CI, 0.19–0.99). The safety outcomes were similar in both the groups as major bleeding events were comparable (6% vs. 4%, respectively, HR 1.83, 95% CI, 0.68–4.96). CRNMB was reported in 12.3% of patients in the rivaroxaban group vs 3.4% of patients in the

dalteparin group. Also, no difference in overall survival was found in both groups. Hence, the trial had reported the noninferiority of rivaroxaban with respect to dalteparin in patients with cancer and VTE.

There are other trials under the CALLISTO program that are currently ongoing, like the CONKO-011, COSIMO, and CASTA-DIVA IIR trials. Brief summaries of these trials are tabulated in table 2.

**Table 2.** List of ongoing studies under CALLISTO program

Name of study	Trial no.	Patient type	Experimental drug	Comparator drug	Objectives	Status
CASTA- DIVA	NCT02746185	Patients with active cancer and symptomatic pulmonary embolism, proximal deep vein thrombosis, iliac or caval thrombosis	Rivaroxaban: 15 mg orally twice daily for 3 weeks followed by 20 mg once daily for 9 weeks	Dalteparin 200 IU/kg SC once daily for one month followed by 150 IU/kg SC once daily for 2 months	Comparing the efficacy and safety of oral rivaroxaban and subcutaneous dalteparin in patients with cancer-associated thrombosis	Data collection for the primary outcome was completed in 2018. Results yet to be published
COSIMO	NCT02742623	Female and male patients with active cancer and a diagnosis of DVT/ and/or PE after the decision for treatment with rivaroxaban	Rivaroxaban	Shifting from LMWH and/or VKA	Collecting prospective real-world data on patient satisfaction with anticoagulation treatment after a switch from LMWH or VKA to rivaroxaban in patients with cancer	Completed in February 2020, results yet to be published
CONKO-011	NCT02583191	Tumor patients with active cancer and newly diagnosed thromboembolic events	Rivaroxaban: 15 mg twice daily for 21 days, followed by 20 mg once daily over a period of 3 months	Enoxaparin: 1 mg/kg BW twice daily Tinzaparin: 175 I.E./kg BW once daily Dalteparin: 200 I.E./kg BW once daily	Showing feasibility (efficacy and safety) of Rivaroxaban in the treatment of VTE in cancer patients in comparison to the standard treatment with low molecular weight heparin	Ongoing
FRONTLINE 2		Patients with active cancer and PE/DVT	NA	NA	Evaluation of how clinicians perceive the risk of VTE in cancer patients and to provide insight into current strategies for thrombo-prophylaxis and management	Ongoing

Data was obtained from the Cochrane library and clinicaltrials.org databases.

#### 4.5. Challenges with DOAC Therapy in Cancer Patients

The pharmacokinetics of different DOAC agents are dependent on their differential renal clearance (dabigatran 80%, edoxaban 50%, rivaroxaban 33%, and apixaban 27%) [22]. Being subject to nephrotoxic chemotherapeutic agents, cancer patients have an increased prevalence of chronic kidney disease (CKD) [23]. Patients with advanced kidney disease should be opted out of any form of DOAC to an alternative anticoagulant that is less dependent on renal clearance.

The next major clinical challenge in DOAC therapy is cancer-associated thrombocytopenia. In such patients, it is usually recommended to discontinue anticoagulation if the platelet count falls below 50,000/ml [24].

The metabolism of DOAC is differentially mediated via cytochrome P450 (CYP) enzyme system [25] and its uptake is mediated by the P-glycoprotein (P-gp) system [26]. Some adjunctive cancer therapies, such as anti-emetics, opioids, and antibiotics, are capable of altering CYP3A4 metabolism [27]. Administration of DOAC is not recommended in conjunction with therapies that are considered strong inducers or inhibitors of P-gp. Hence, selecting the right DOAC for the right patient is a major concern for a clinician, and it might require interdisciplinary communication.

## 5. Conclusion

The results from previous studies comparing VKA to LMWH and studies comparing LMWH to DOAC in adult cancer patients with VTE have led several clinical guidelines including The American Society of Clinical Oncology (ASCO), The International Society on Thrombosis and Haemostasis (ISTH), and The International Initiative on Thrombosis and Cancer (ITAC) to recommend DOAC as the preferred treatment for cancer-associated thrombosis in patients with non-gastrointestinal and non-gastrourinary cancers who are at low risk of bleeding.

Among those with gastrointestinal or gastrourinary cancer-associated thrombosis, LMWH are preferred. VKA can be considered if patients are not candidates for LMWH or DOAC, particularly for those with stable disease and those in remission. The optimal duration of therapy is still unclear, but previous and current guidelines recommend at least 6 months of therapy for cancer-associated thrombosis. A longer duration of anticoagulation may be considered if the patient has active cancer or is actively receiving antineoplastic therapy.

From the author's experience, DOAC are currently preferred as first-line therapy for cancer-associated thrombosis in patients with non-gastrointestinal and non-gastrourinary cancers who have a low risk of intracerebral hemorrhage, and can take oral medications.

Patients with primary brain cancers or brain metastases need to be reviewed carefully to address crucial points prior to initiating anticoagulation, such as the lack of survival benefit, the benefits of using inferior vena cava filters, and the risk of intracerebral hemorrhage. It is highly recommended to involve patients with malignancies and VTE in decisions on anticoagulation due to the complexity of factors affecting decision-making in those patients.

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## Conflict of Interest

The author declares no conflict of interest.

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