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# Challenging issues in the management of cancer-associated venous thromboembolism

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**Abstract**

Venous thromboembolism (VTE) is a common complication among patients with cancer and is associated with delays in underlying cancer treatment and increases in morbidity and mortality. Acute and long-term treatments with low-molecular-weight-heparin (LMWH) have been recommended as a standard of care for patients with cancer with VTE for the past 20 years. Direct oral anticoagulants (DOACs) have recently emerged as a new therapeutic modality for cancer-associated VTE because of the convenience of oral administration and rapid onset of action. Our knowledge regarding DOACs for cancer-associated VTD has expanded in recent years. Thus, this study aimed to review recent major pivotal trials comparing DOACs with LMWH for managing cancer-associated VTE. Moreover, a recently updated understanding of DOACs in the treatment of cancer-associated VTE in specific challenging situations is presented.

**Key Words** Cancer, Direct oral anticoagulant, Venous thromboembolism

## INTRODUCTION

Venous thromboembolism (VTE) is one of the major complications in patients with cancer, with a four to seven-fold higher risk than healthy individuals. Furthermore, it is the second leading cause of death in patients with cancer following underlying malignant disease progression [1-3]. In addition, patients with cancer-associated VTE had three times increased risk of hospitalizations, and the treatment of whom is frequently associated with delay or discontinuation of chemotherapy for underlying cancer treatment [4, 5]. Moreover, VTE developing in patients with cancer is also associated with two to six times increased risk in mortality [5]. Thus, prompt diagnosis and optimal therapeutic strategies for VTE in patients with cancer are essential in appropriately managing patients with cancer.

However, despite the appropriate anticoagulation treatment in cancer-associated VTE, patients with cancer are associated with a relatively higher risk of complications, such as recurrent VTE and major bleeding, than those without cancer [2, 6]. Over the past 20 years, low-molecular-weight-heparins (LMWHs) have been recommended as a standard of care for acute and long-term treatment of cancer-associated VTE based on the landmark trials comparing LMWHs to a vitamin K antagonist [7, 8]. Direct oral anticoagulants (DOACs) are attractive new therapeutic drugs for treating VTE in patients with cancer because of the convenience of oral administration, rapid onset of action, and predictable efficacy and safety [9]. Recently, large randomized phase 3 trials evaluating the effectiveness and safety of direct oral anticoagulants (DOACs) compared to LMWH in treating cancer-associated VTE have been reported [10-13]. In this review, we summarize the results of these pivotal trials and highlight the role of DOACs in some challenging clinical situations, including the treatment of VTE in patients with gastrointestinal cancer; drug-drug interaction; thrombocytopenia; renal dysfunction, which might be unmet medical needs in the management of cancer-associated VTE.

## MAJOR PIVOTAL TRIALS OF DOACS IN CANCER-ASSOCIATED VTE

The standard therapy for VTE in patients with cancer has been LMWH over the past 20 years [14-16]. Prospective randomized trials, such as Hokusai VTE Cancer [10], SELECT-D [11], ADAM VTE [13], and CARAVAGGIO [12], evaluating the efficacy and safety of DOACs and LMWH

for treating VTE in patients with active cancer have been recently reported. The Hokusai VTE Cancer trial was conducted to determine whether edoxaban treatment for 6–12 months was non-inferior to dalteparin therapy in 1,050 patients with cancer-associated acute symptomatic or incidentally detected VTE [10]. The primary endpoint was the composite of recurrent VTE or major bleeding 12 months after randomization. Edoxaban was administered 60 mg orally once a day; however, if the bodyweight was <60 kg or creatinine clearance was 30–50 mL/min, it was reduced to 30 mg per day. The primary outcomes of recurrent VTE or major bleeding were 12.8% and 13.5% in the edoxaban and dalteparin groups, respectively, demonstrating that edoxaban was non-inferior to dalteparin (HR, 0.97; 95% CI, 0.70–1.36). A slightly reduced risk of recurrent VTE has been observed in patients who received edoxaban (6.5% vs. 10.3%). However, a significantly increased risk of major bleeding was observed in the edoxaban-treated group (6.3% vs. 3.2%), related to an increased risk of upper gastrointestinal bleeding in patients with gastrointestinal cancers [17]. The SELECT-D study compared oral rivaroxaban with dalteparin injection to treat cancer-associated VTE [11]. Rivaroxaban 15 mg was administered twice a day for the first 3 weeks and then 20 mg was administered once a day for 6 months. The primary endpoint of the 6-month risk of recurrent VTE was 4% and 11% with rivaroxaban and dalteparin, respectively (HR, 0.43; 95% CI, 0.19–0.99). The risk of major bleeding was not different between the two groups (6.0% vs. 4.0%; HR, 1.83; 95% CI, 0.68–4.96), but the risk of clinically relevant non-major bleeding was higher with rivaroxaban (13% vs. 4%). Notably, patients with esophageal and gastroesophageal cancer were excluded during the trial because of the higher risk of major bleeding in patients with those cancers receiving rivaroxaban. The largest randomized trial, the CARAVAGGIO trial, compared oral apixaban therapy with dalteparin therapy for 6 months in 1,170 patients with cancer-associated acute symptomatic or incidentally detected VTE. Apixaban was administered twice a day for 10 mg in the first week and 5 mg for 6 months. The recurrent VTE was compared as a primary endpoint, 5.6% with apixaban and 7.9% with dalteparin. In terms of major bleeding, there was no difference between the two groups with 3.8% apixaban group and 4.0% dalteparin group (HR, 0.82; 95% CI, 0.40–1.69). Another randomized trial, the ADAM VTE trial, evaluating apixaban for treating cancer VTE, was recently published [13]. The primary endpoint of this study was major bleeding as a measure of safety in 287 patients with cancer with VTE, which occurred in 0% and 1.4% of patients in the apixaban and dalteparin arms, respectively. Recurrent VTE was significantly lower in the apixaban arm than in the dalteparin arm (0.7% vs. 6.3%). Notably, this study included different types of qualifying VTE for enrollment, including upper extremity, splanchnic vein, and cerebral vein thrombosis, which were not eligible in other pivotal trials.

The results of Hokusai VTE Cancer and SELECT-D trials revealed that DOACs reduce the risk of recurrent VTE but increase the risk of bleeding complications, particularly in patients with gastrointestinal cancers [10, 11, 17]. Results of a meta-analysis support these observations [18, 19]. In

**Table 1.** Study characteristics of major pivotal trials comparing DOAC with LMWH.

| | Hokusai VTE Cancer | SELECT-D | ADAM VTE | CARAVAGGIO |
|---|---|---|---|---|
| Trial design | Non-inferiority phase 3 | Pilot | Superiority phase 3 | Non-inferiority phase 3 |
| Sample size | 1,046 | 406 | 287 | 1,155 |
| DOAC arm | LMWH for 5 days then edoxaban 60 mg/day PO | Rivaroxaban 15 mg PO twice a day for 21 days, then 20 mg PO once a day | Apixaban 10 mg PO twice a day for 7 days, then 5 mg PO twice a day | Apixaban 10 mg PO twice a day for 7 days, then 5 mg PO twice a day |
| LMWH arm | Dalteparin 200 U/kg daily for 1 month followed by 150 U/kg daily | | | |
| Dose reduction of DOAC | Edoxaban 30 mg/day PO in patients with <60 kg of body weight; creatinine clearance 30–50 mL/min; drug-to-drug interactions | N/A | N/A | N/A |
| Treatment duration | 12 months | 6 months | 6 months | 6 months |
| Type of qualifying VTE | Acute symptomatic or incidentally detected lower extremity proximal DVT or PE of segmental or more proximal pulmonary artery | Acute symptomatic lower extremity proximal DVT, symptomatic PE, or incidental PE | Acute lower extremity or upper extremity DVT, PE, splanchnic vein, or cerebral vein thrombosis | Acute symptomatic or incidentally detected lower extremity proximal DVT or PE of segmental or more proximal pulmonary artery |
| Cancer excluded | Basal cell/squamous cell cancer of the skin | Basal cell/squamous cell cancer of the skin<br>Esophageal or gastroesophageal cancer | Basal cell/squamous cell cancer of the skin | Basal cell/squamous cell cancer of the skin<br>Primary brain tumor<br>Intracerebral metastasis<br>Acute leukemia |
| Primary outcome | Composite of recurrent VTE or major bleeding | Recurrent VTE | Major bleeding | Recurrent VTE<br>Major bleeding |

contrast, the CARAVAGGIO trial showed that apixaban resulted in a similar risk of recurrent VTE without increasing the risk of major bleeding [12, 20]. However, it is noteworthy that patients with high bleeding risk features (i.e., central nervous system metastasis, hematologic malignancies such as leukemia, and platelet <75,000/μL) were excluded from this study. In addition, only approximately 4% of enrolled patients had primary cancer in the upper gastrointestinal tract, a major site of bleeding complications in other trials. The key differences in study design between these pivotal trials are summarized in Table 1. Based on these results, DOACs such as edoxaban, rivaroxaban, and apixaban were non-inferior to LMWH in preventing recurrent VTE and might be used for acute and long-term treatment of VTE in patients with cancer.

## SPECIFIC SITUATIONS THAT NEED TO BE CONSIDERED WHILE ON USE OF DOACS IN CANCER-ASSOCIATED VTE

### Gastrointestinal cancers

The Hokusai VTE Cancer trial [10, 17] and the SELECT-D trial [11] reported that patients with DOACs had a higher risk of major bleeding than those with LWMH. In the Hokusai VTE Cancer trial, a high incidence of major bleeding in the edoxaban group was associated with a high rate of upper gastrointestinal bleeding in patients with gastrointestinal cancers who received edoxaban [17]. Upper gastrointestinal bleeding occurred in 14% of all major bleedings in the dalteparin group and 47% of all major bleeding complications in the edoxaban group. Similar results were observed in the SELECT-D trial [11], and approximately 45% of all major bleeding events in the rivaroxaban group were upper gastrointestinal bleeding. However, in the CARAVAGGIO trial, there was no difference in the incidence of gastrointestinal bleeding in patients with major bleedings who received dalteparin (10/23, 43.5%) and apixaban (11/22, 50.0%) [12, 20].

Identifying risk factors for gastrointestinal bleeding after DOACs may help guide the use of anticoagulants in treating these patients. In the nested case-control study within the Hokusai VTE Cancer cohort, advanced cancer and hemoglobin <10 g/dL were associated with an increased risk of gastrointestinal bleeding in patients with gastrointestinal cancer receiving edoxaban [21]. There may be differences in the risk of gastrointestinal bleeding depending on the characteristics of underlying cancer, patients, and DOACs. Therefore, when clinicians use DOACs, particularly rivaroxaban and edoxaban, to treat VTE in patients with gastrointestinal cancer, attention should be paid to their use if they have high-risk characteristics for gastrointestinal bleeding (i.e., advanced cancer and low hemoglobin levels).

### Drug-drug interaction

Compared to warfarin, DOACs have little interaction with food and drugs, one of the major advantages of DOACs. However, data have recently suggested that DOACs interact with other drugs and that these interactions are associated with an increased risk of actual bleeding complications [22, 23]. In particular, taking DOACs with CYP3A4 and P-glycoprotein strong inducers or inhibitors together may increase or decrease blood concentrations of DOACs by drug-drug interaction, which may increase the risk of bleeding complications and recurrent VTE [24, 25]. In addition, a recent study using the Korean Health Insurance Review and Assessment database found that many drugs that can cause drug-drug interaction were prescribed with DOACs in real-world practice and that the risk of bleeding complications was increased as the concomitant use of drugs that can cause interaction was increased, requiring attention in drug-drug interaction when DOACs were used [26].

### Thrombocytopenia

Thrombocytopenia, defined as platelet counts of <100,000/μL, is a frequently observed complication in patients with cancer and associated with either adverse events of anti-cancer therapy or the underlying disease itself, affecting a substantial number of patients on chemotherapy. This increases the risk of bleeding complications in patients with cancer-associated VTE, but the risk of recurrent VTE was not reduced [27, 28]. The main consideration for VTE treatment in these patients with cancer with thrombocytopenia is balancing the risk of such bleeding complications and the recurrent VTE. According to the recent recommendation from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [29], LMWH is the preferred anticoagulant for treating acute cancer-associated VTE with thrombocytopenia, and full-dose anticoagulation is recommended if platelet counts are ≥50,000/μL. However, once platelet counts decline <50,000/μL, treatment strategies should be based on the degree of thrombocytopenia, VTE type, and recurrence risk. If patients have symptomatic segmental or more proximal PE, proximal DVT, or recurrent VTE, full-dose anticoagulation with transfusion support to maintain platelet counts >50,000/μL is suggested. In contrast, it is feasible to administer a half or the prophylactic dose of LMWH in patients with low-risk features for recurrence (i.e., incidental subsegmental PE or isolated distal DVT, or subacute or chronic VTE). For patients with platelet levels <25,000/μL, temporary anticoagulation discontinuation should be considered in any circumstance. There is a lack of data on the use of DOACs in patients with cancer-associated VTE and thrombocytopenia because major pivotal trials of DOACs on cancer-associated VTE did not include patients with platelet counts <50,000–100,000/μL at baseline [11, 30-32]. In a recent small multicenter prospective study evaluating the risk of hemorrhage and recurrent VTE in patients with cancer-associated VTE and concurrent thrombocytopenia (platelet counts <100,000/μL) [33], modified dose anticoagulation, including 2.5 mg apixaban twice daily and 10 mg rivaroxaban daily, has shown to be a safe alternative approach. Thus, DOACs are urgently needed to be investigated in patients with cancer with VTE

in the setting of thrombocytopenia.

### Renal dysfunction

As a substantial proportion of absorbed DOACs is eliminated via the kidney, the administration of DOACs at the recommended usual dose in patients with severe renal impairment (i.e., creatinine clearance <30 mL/min) may be associated with drug accumulation and enhanced anticoagulant effects, leading to an increased risk of bleeding complications [34]. Therefore, cancer patients with creatinine clearance <30 mL/min were excluded from the major pivotal trials for DOACs [11, 30-32], and the clinical evidence for the use of DOACs in patients with severe renal impairment or on dialysis remains still uncertain. Thus, current guidelines for cancer-associated VTE recommend using unfractionated heparin followed by warfarin or LMWH adjusted to anti-factor Xa activities in patients with severe renal impairment [35, 36].

However, growing laboratory data show substantial differences in uptake, metabolism, and elimination of DOACs [37]. In particular, the renal excretion rate of absorbed apixaban was approximately 27%, which was substantially lower than that of other DOACs (dabigatran 80%, edoxaban 50%, rivaroxaban 35%), suggesting the different effects of apixaban on bleeding complications in patients with severe renal impairment. In addition, clinical experiences of apixaban in atrial fibrillation for stroke prevention have reported that the risk of bleeding after patients with severe renal impairment or those on dialysis received apixaban is comparable with that observed after patients received warfarin [38]. Finally, the AHA/ACC/HRS updated atrial fibrillation guideline recommends that apixaban be administered without dose reduction in patients with severe renal impairment or those on dialysis [39]. Therefore, further research on apixaban is needed in patients with cancer-associated VTE and severe renal impairment.

## CONCLUSION

Treatment of VTE in patients with cancer is challenging because of its high risk of recurrence and bleeding complications. Thus, it requires careful consideration of various issues surrounding patients and cancer-associated VTE itself. Based on the evidence presented, DOACs represent a reasonable treatment option for cancer-associated VTE and can be advantageous in patients with cancer because of improved patients' preferences and quality of life as well as efficacy and favorable toxicities. However, further research is still needed to individualize treatment strategies in patients with cancer with VTE based on bleeding and recurrence risk, renal function, and drug-drug interactions with concomitant chemotherapy.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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