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The use of direct oral anticoagulants in the treatment of acute venous thromboembolism in cancer patients

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Abstract

Introduction – After the CLOT study, LMWHs (low-molecular weight heparins) have gradually replaced warfarin as the treatment of choice for VTE (venous thromboembolism) in cancer patients. Randomized controlled studies comparing DOACs (direct oral anticoagulants) to LMWHs in cancer patients are still limited. However, new emerging data are supporting the use of DOACs in cancer-associated thrombosis.

Areas Covered — This review will discuss the recent studies that addressed the utilization of such agents in the treatment of VTE in cancer patients. It will also address challenges that can be encountered while using these agents particularly in cancer patients.

Expert Commentary — Up until the Hokusai VTE Cancer study, data on the use of DOACs in cancer patients have been limited but supportive of their use in such patients. The Hokusai VTE Cancer study shows that edoxaban is non-inferior to dalteparin in prevention of recurrent VTE but at expense of higher major bleeding namely in patients with gastrointestinal cancer. Although further studies involving other DOACs may reinforce the efficacy of DOACs in this population of patients, studies looking at subpopulation of cancer patients may be of more clinical value to clinicians who are trying to balance between treatment of thrombosis and risks of bleeding.

Key words: Direct oral anticoagulants (DOACs), dabigatran, apixaban, edoxaban, rivaroxaban, low molecular weight heparins (LMWHs), venous thromboembolism (VTE)

1. Introduction

Cancer patients are at much higher risk for thromboembolic events [1]. In addition to their existing comorbidities, cancer itself and its treatments, both surgical interventions and chemotherapy, contribute significantly to this risk [2]. In a recent observational cohort study using the UK Clinical Practice Research Datalink, researchers identified a total of 6,592 active-cancer-associated venous thromboembolic events among 112,738 cancer-associated person-years of observation. The incidence rate of first venous thromboembolism (VTE) in patients with active cancer was 5.8 [95 % confidence interval (CI), 5.7-6.0] per 100 person-years [3]. Additionally, several studies had clearly shown that the survival of cancer patients complicated by VTE is significantly lower than those without [4]. In a large study using the Danish Cancer Registry, the one-year survival rate for cancer patients with VTE was significantly lower than those without (12% compared to 36%, $p<0.001$) [5]. Another retrospective cohort study that used the discharge database of 66,106 adult neutropenic cancer patients with 88,074 hospitalizations at 115 medical centers in the United States reached similar conclusions [6].

Additionally, VTE can negatively affect the quality of life of such patients and may result in significant delays in delivering chemotherapy or even performing surgical interventions [7]. Treatment of VTE in patients with active cancer is always problematic; balancing the risk of VTE recurrence and bleeding complications can be challenging [8]. In this review, we discuss the recent studies that addressed the utilization of DOACs in the treatment of VTE in cancer patients. We will also address the many challenges that can be encountered while using these agents particularly in cancer patients.

2. Methods

In this review, we discuss the clinical utilization of the new oral anticoagulants, limitations and licensed indications. We will also discuss the results of clinical trials testing these agents in the treatment of cancer associated VTE. With this objective, we searched Medline (up to December 2017) and clinical

trial registries (i.e., clinicaltrials.gov) using the terms “cancer”, “anticoagulation”, “rivaroxaban”, “apixaban”, “edoxaban”, “betrixaban”, and “dabigatran”. Case-reports and articles published in languages other than English were excluded. We also searched regulatory agency websites (US Food and Drug Administration, European Medicines Agency) and relevant conference proceedings.

3. Current VTE treatment options in cancer patients

Low molecular weight heparins (LMWHs) have been the standard treatment for cancer-associated thrombosis. In a landmark study (CLOT trial), 672 patients with cancer and acute symptomatic VTE were randomly assigned to receive dalteparin at a dose of 200 IU/Kg subcutaneously once daily for 5-7 days and a coumarin derivative for six months or dalteparin alone for six months (200 IU/Kg once daily for one month, followed by a daily dose of 150 IU/Kg for five months). During the 6-month study period, 8.0% of the patients in the dalteparin group had recurrent VTE compared to 15.8% patients in the coumarin group (hazard ratio (HR), 0.48; 95% confidence interval (CI), 0.30-0.77, p=0.002). No significant difference between the two groups in the rates of major bleeding or any bleeding [9].

Currently, LMWHs are endorsed by many international guidelines including the European Society of Medical Oncology (ESMO) [10], American College of Chest Physicians (ACCP) [11], the American Society of Clinical Oncology (ASCO) [12] and the National Comprehensive Cancer Network (NCCN)[13].

However, the requirement of daily subcutaneous injections makes LWMH inconvenient to use and compliance may be an issue to some patients.

Moreover, aside from their problematic use in renal insufficiency due to their renal clearance, cost is an obstacle that limit their use in many countries. Although Heparin-induced thrombocytopenia (HIT) occurs at a lower rate with LMWHs when compared to UFH, when it occurs, it constitutes a high risk in terms of morbidity and mortality.

4. Oral anticoagulants

Warfarin, which was introduced initially as a pesticide against rats and mice and then as anticoagulant for human use in 1954 [14], has been the most commonly used oral anticoagulant worldwide. However, its long half-life with slow onset and slow offset of action, relatively narrow therapeutic index, and its multiple drug and dietary interactions result in significant inconvenience in its routine use. Additionally, the need for frequent laboratory monitoring offset their low direct cost.

Ximelagatran, another oral anticoagulant that directly inhibit thrombin, was licensed in Europe for a short time then was withdrawn in 2006 for concerns of hepatotoxicity [15].

The continued quest for an "ideal anticoagulant" led to the introduction of so called “New/Novel” or “Direct” oral anticoagulants (NOACs or DOACs). These drugs act by inhibiting factor-Xa (apixaban, rivaroxaban, edoxaban) or by directly inhibiting thrombin (dabigatran).

Direct oral anticoagulants have been vigorously evaluated in many large-scale clinical trials for various clinical indications and are increasingly used in stroke prevention in patients with atrial fibrillation, and thromboprophylaxis in patients undergoing major orthopedic procedures [16].

Additionally, DOACs were thoroughly investigated in the acute treatment of both DVT and PE. Dabigatran has been evaluated for VTE treatment in RE-COVER [17], RE-COVER II [18], RE-MEDY [19] and RE-SONATE [20] trials. Rivaroxaban was evaluated in EINSTEIN-DVT [21], EINSTEIN-PE [22], EINSTEIN-Extension [23] and EINSTEIN-CHOICE [24] trials. Similarly, apixaban was evaluated in the AMPLIFY-VTE [25] and AMPLIFY-EXTENSION [26] trials while edoxaban was evaluated in the HOKUSAI-VTE trial [27]. All trials had shown that DOACs are at least as effective and as safe as warfarin for this indication. A summary of the largest studies are listed in table-1. Based on the results of these trials, the United State Food and Drug Administration (FDA) had approved their use for treatment of both DVT (deep vein thrombosis) and PE (pulmonary embolism). However, little data is known about

their utilization in ~~active~~ treatment of VTE in cancer patients. Despite that, many clinicians around the world are using DOACs off-label in cancer patients due to the many reasons mentioned before.

The fact that such agents are given orally, at a fixed-dose without a need for laboratory monitoring is attractive, both to patients and physicians, alike. However, these agents are not without problems, either.

All new oral anticoagulants are partially excreted by the kidneys, so careful monitoring of creatinine clearance (CrCl) is mandatory to avoid toxicity. Dabigatran with its 80% renal excretion is contraindicated in severe renal insufficiency, defined by a CrCl level of lower than 30 ml/min and a dose reduction is recommended when the CrCl is between 30 and 50 ml/min. On other hand, only a third of rivaroxaban and 50% of edoxaban are cleared by the kidneys and as such can be used in nonvalvular atrial fibrillation patients with severe renal insufficiency, defined by a CrCl level between 15 and 29 ml/min [28,29], while for rivaroxaban it is recommended to avoid its use in patients treated for acute DVT/PE with CrCl < 30 ml/min. Apixaban, on the other hand, can be used in patients with CrCl as low as 15 ml/min.

Hepatobiliary metabolism is an important factor in the clinical utilization of DOACs. Rivaroxaban metabolism involves CYP3A4 and drug-drug interactions are quite likely if inhibitors and inducers of CYP3A4 are concomitantly used. Although CYP3A4 has no role to minimal role in dabigatran and Edoxaban metabolism, it serves as a substrate for P-glycoprotein (P-gp). All DOACs are P-gp substrates and as such changes in ~~its~~ their bioavailability can be expected if other drugs that are strong P-gp inhibitors, such as ketoconazole, amiodarone, verapamil, quinidine and clarithromycin, or inducers such as rifampicin are used [30], Table 2.

5. Direct oral anticoagulants in cancer patients

Data on the use of DOACs in cancer patients is very limited. The number of cancer patients enrolled in the large clinical trials of DOACs in the treatment of VTE is very small. However, several follow up

publications pooled and analyzed data related to the utilization of DOACs in the treatment of both DVT and PE in cancer patients enrolled in these trials, Table-3.

Data on dabigatran were extracted from two major randomized double-blind clinical trials; RECOVER [17] and RECOVER II [18]. There were no significant differences in VTE recurrence rates or VTE-related deaths between dabigatran (3.5%) and warfarin (4.7%) in patients with cancer at baseline (HR 0.74; 95 % CI, 0.20-2.7). Major bleeding events were significantly more in patients with cancer at any time (4.2%) than in patients without cancer (1.1 %, HR 4.09; 95 % CI, 2.22–7.53). Additionally, major or clinically relevant non-major bleeding was also more frequent with cancer (13.8 %) than non-cancer patients (5.5 %; HR 2.78; 95 % CI, 2.01–3.84). However, there was no difference in major bleeding in patients with cancer at baseline treated with dabigatran (3.8%) or those treated with warfarin (3.0%, HR1.23; 95% CI, 0.28-5.5) [31].

EINSTEIN-DVT and EINSTEIN-PE are two clinical trials that tested the value of rivaroxaban in the treatment of VTE. Data on cancer patients enrolled in both studies were collected and analyzed separately. A total of 655 patients with active cancer (either at baseline or diagnosed during the study) were identified. Venous thromboembolism recurred in 16 (4.5%) of 354 patients treated with rivaroxaban compared to 20 (6.7%) of 301 other patients treated with enoxaparin and vitamin K antagonists (HR 0.67; 95% CI, 0.35-1.30). Clinically relevant bleeding was encountered in 48 (13.6%) of 353 patients receiving rivaroxaban and in 49 (16.4%) of 298 patients receiving standard therapy (HR 0.80; 95% CI, 0.54-1.20). Major bleeding was encountered in 8 (2.3%) patients receiving rivaroxaban compared to 15 (5.0%) patients receiving standard anticoagulation (HR 0.42; 95% CI, 0.18-0.99). In both studies, there were a total of 469 patients with prior history of cancer. The VTE recurrence rate was similar among patients treated with rivaroxaban (n=233) and those treated with a LMWH and Vitamin-K antagonist (n=236); 2% each. This VTE recurrence rate was also similar (2%) to majority of enrolled patients (n=3563) without cancer [32].

In the AMPLIFY trial [25], 169 (3.1%) of the 5,395 originally randomized patients had active cancer at baseline and 365 (6.8%) had a history of cancer (without active cancer) at the time of randomization. Recurrent VTE was lower among patients with active cancer treated with apixaban (3.7%) compared to 6.4% of patients treated with enoxaparin/warfarin (HR 0.56; 95% CI, 0.13-2.37). Similar trend was also noted among the group of patients with previous history of cancer; VTE recurred in 1.1% in the apixaban group and 6.3% in the enoxaparin/warfarin groups (HR 0.17; 95% CI, 0.04-0.78). Major bleeding was lower in active cancer patients treated with apixaban (2.3%) compared to 5.0% in those treated with enoxaparin/warfarin (HR 0.45; 95% CI 0.08-2.46). Such lower incidence of bleeding was also noted among patients with prior history of cancer; major bleeding episodes were encountered in 0.5% in the apixaban group and 2.8% in the enoxaparin/warfarin group (HR 0.20; 95% CI 0.02-1.65) [33].

Vedovati and colleagues had recently published a systemic review and a meta-analysis that included the six trials that compared DOACs versus conventional anticoagulants. A total of 1,132 patients with cancer were included. VTE recurrence occurred in 23 of 595 (3.9%) treated with DOACs and in 32 of 537 (6.0%) patients treated with conventional anticoagulants (HR 0.63; 95% CI, 0.37-1.10). Major bleeding occurred in 3.2% and 4.2% of patients receiving DOACs and conventional treatment, respectively (HR 0.77; 95% CI, 0.41-1.44) [34].

A prespecified subgroup analysis and a post-hoc analysis of non-inferiority and safety of edoxaban in the treatment of VTE in cancer patients enrolled in the randomized, double-blind, multicenter, HOKUSAI-VTE trial [27] was performed. Of the 771 patients with cancer enrolled in the original trial, 378 were treated with edoxaban and 393 were treated with warfarin. Recurrent VTE occurred in 14 (3.7%) patients in the edoxaban group and in 28 (7.1%) patients treated with warfarin (HR 0.53; 95% CI 0.28-1.00; p=0.0007). Major or clinically relevant non-major bleeding occurred in 47 (12.5%) patients treated with edoxaban versus 74 (18.8%) patients treated with warfarin (HR 0·64; 95% CI 0·45-0·92; p=0·017) [35].

Recently, the Hokusai VTE Cancer Investigators conducted an open-label, multicenter, randomized non-inferiority trial comparing edoxaban to dalteparin in adult cancer patients (N= 1050, predominantly advanced cancer) with acute symptomatic or incidental DVT (popliteal, femoral, iliac or inferior vena cava) or PE. Patients in the edoxaban arm were given a LMWH (physician choice) initially for at least 5 days then edoxaban 60 mg daily (30 mg if CrCl 30-50 ml/min or weight of 60 kg or less). Patients in the dalteparin arm received dalteparin subcutaneous 200 IU per kilogram of body weight once daily for 30 days with a maximum daily dose of 18,000 IU. Then, dalteparin was given at a dose of 150 IU per kilogram once daily. In all patients, treatment was given for at least 6 months and up to 12 months as determined by the treating physician. The primary endpoint was a composite of recurrent VTE or major bleeding and the minimum duration of follow-up was 9 months. Recurrent VTE or major bleeding occurred in 12.8% of patients in the edoxaban arm compared to 13.5% in the dalteparin arm (HR 0.97, p=0.006 for non-inferiority and p=0.87 bullet 4for superiority). Recurrent VTE occurred in 7.9% of patients in the Edoxaban arm versus 11.3% in the dalteparin arm (HR 0.71, p=0.09). However, major bleeding occurred in 6.9% of patients in the edoxaban arm as compared to 4.0% in the dalteparin arm with difference being statistically significant (HR 1.77, p=0.04). In a subgroup analysis, patients with gastrointestinal cancer were more likely to have major bleeding with edoxaban compared to dalteparin (13.2% vs 2.4% respectively, p=0.0169). Genitourinary bleeding was higher in patients on edoxaban, too [36].

Many ongoing clinical trials are testing the efficacy and safety of these new anticoagulants specifically in cancer patients. The CAP trial, is a single-arm, phase IV trial, testing apixaban as treatment of VTE in cancer patients. Patients with a confirmed diagnosis of cancer and objectively verified VTE will be treated with apixaban 10 mg twice daily for 1 week, then 5mg twice daily for 6 months, then 2.5 mg twice daily for as long as the treating physician finds it necessary. Recurrent objectively confirmed VTE or death related to VTE and major or clinically relevant non-major bleeding are the primary endpoints [37].

Two similarly-designed ongoing phase III, randomized, open label studies; one in the US (NCT02585713) [38] and the other is conducted across Europe (CARAVAGGIO) [39]. Both are testing apixaban against dalteparin in cancer patients with VTE. Both study medications are given for 6 months.

Several other ongoing studies are testing rivaroxaban in various clinical conditions. The PRIORTY study is an open label, multi-center, and randomized phase II trial designed to compare the safety and efficacy of rivaroxaban against subcutaneous dalteparin in patients with acute VTE and upper gastrointestinal, hepatobiliary, or pancreatic cancers. Rivaroxaban will be given at 15 mg orally twice daily for 3 weeks followed by 20 mg once daily for 21 weeks [40]. The CASTA-DIVA study is another ongoing non-inferiority open label randomized multicenter trial designed to compare rivaroxaban and dalteparin in patients with active cancer and acute symptomatic VTE. Both the experimental and control treatments will be given for three months [41].

The ongoing CANVAS study is taking a different approach. The study is comparing any of the DOACs (edoxaban, apixaban, rivaroxaban, or dabigatran) with any LMWH (dalteparin, enoxaparin) or fondaparinux with or without warfarin. Both treatment arms will be given for 6 months [42]. Many other studies [43-45], including CONKO-011 [43] and COSIMO [44], are ongoing and utilizing the DOACs are summarized in Table 4.

6. Reversal of DOACs

The lack of a specific antidote to DOACs (except dabigatran) is a major concern in cancer patients who are at higher risk for bleeding and are frequently subjected to invasive diagnostic and therapeutic procedures; some of which can be urgent. Prothrombin complex concentrate (PCC), activated PCC and recombinant activated factor VII (rFVIIa) are reasonable options to bypass the anticoagulant effects of DOACs [46,47].

Because of dabigatran's lipophilic structure and because significant fraction is not protein bound, hemodialysis theoretically can be used in the reversal of dabigatran associated major bleeding. On the other hand, both apixaban and rivaroxaban are highly protein bound rendering them not dialyzable [48].

Idarucizumab, a monoclonal antibody fragment, was developed to reverse the anticoagulant effect of dabigatran. In a recently-published prospective, open-label study, 301 patients with active bleeding (gastrointestinal or intracranial) and 202 others planned to have an urgent invasive procedure while on dabigatran were treated with 5 g of intravenous idarucizumab. The median maximum percentage reversal of dabigatran was 100% (95% CI, 100-100). The median time to the cessation of bleeding was 2.5 hours while the median time to the initiation of the intended invasive procedure was 1.6 hours [49]. Based on this data, idarucizumab received global approval (including FDA, EMA, Health Canada) as the first reversal agent for the anticoagulant effect of dabigatran [50]. However, the cost of this reversal agent can exceed $3,000.

Andexanet alfa is a specific antidote for direct (rivaroxaban, apixaban, and edoxaban) and indirect factor Xa inhibitors (LMWHs and fondaparinux) [51,52]. Ciraparantag is a synthetic water-soluble molecule that was developed to bind heparin, direct factor Xa inhibitors, and thrombin inhibitors. Currently, both andexanet alfa and ciraparantag are under development as specific reversal agents [53].

7. Discussion

Because of their rapid onset of action after oral administration and because of their predictable pharmacokinetics and pharmacodynamics without the need for routine laboratory monitoring for dose adjustment, at least for the majority of patients, DOACs tend to be more attractive to use and may improve compliance to anticoagulation in cancer patients.

It is well known that cancer patients carry a much higher risk of thrombosis than other medically-ill patients [1,2] and recurrence of thrombosis is also more common, too [54,55]. This risk is mitigated by

patient-related factors, the type of cancer, but also by the various treatment modalities the patient goes through during his/her cancer treatment.

Additionally, due to the cancer itself or its therapy, cancer patients are at much higher risk of bleeding while on anticoagulants [54]. Cancer itself may induce mucosal bleeding related to the site involved like gastrointestinal bleeding in gastric or colorectal cancers, hematuria in bladder cancers, vaginal bleeding in uterine or cervical cancers and hemoptysis in lung cancers. Myelosuppressive chemotherapy may also induce significant thrombocytopenia and adds to the risk of bleeding. Surgical procedures and mucosal injury associated with radiation therapy are additional risk factors, too.

The major trials that got DOACs their various indications compared DOACs with Warfarin. Therefore, the subset analysis of cancer-associated VTE in these studies has shown the possible efficacy of DOACs but when compared to warfarin, which is not the standard of care (LMWHs)[10-13]. Therefore, based on these data, using DOACs in patients with cancer-associated VTE would not have been clinically advisable. The Hokusai VTE Cancer study is the first randomized trial that compared a DOAC (edoxaban) to a LMWH (dalteparin) in patients with cancer-associated VTE. It demonstrated noninferiority of edoxaban though with significant higher risk of bleeding in patients with gastrointestinal bleeding. Although the Hokusai study included less metastatic patients, less patients with ECOG 2 and incidental VTE when compared to the CLOT study, it would likely provide a new standard of care option in treating patients with cancer-associated VTE.

Despite the favorable results from various data, there are no data on the differential activity of DOACs in specific subtypes of cancers and treatments. DOACs might have significant interactions with many of the chemotherapeutic agents or other supplementary drugs used in cancer patients namely the antifungal azole agents. Many commonly prescribed drugs induce or inhibit the activity of CYP3A4, the P-glycoprotein transporter, or both. Vinca alkaloids, taxanes, some tyrosine kinase inhibitors, glucocorticoids and some of mammalian target of rapamycin (mTOR) agents are well-known examples

[56]. Moreover, it should be noted that frequent emesis occurring with various chemotherapeutic agents limit the use of DOACs in such patients.

8. Conclusions

Direct oral anticoagulants are increasingly used in the treatment of both DVT and PE. Given its established efficacy and accumulating experience in how to deal with its potential problems, DOACs are becoming an attractive option to utilize in cancer patients. Limited data including subgroup analysis from major trials involving DOACs revealed their effectiveness in this subpopulation of patients. Edoxaban when compared to dalteparin was shown to be non-inferior but associated with higher risk of major bleeding in patients with gastrointestinal cancers. Further trials of other DOACs compared to LMWHs in cancer patients are still pending.

9. Expert Commentary

The current standard of care for the treatment of cancer-associated VTE are LMWHs in general and dalteparin specifically. However, this modality of treatment is associated with the inconvenience of being a subcutaneous injection which could be painful to some patients and also problematic to others (like elderly patients with visual impairments or articulation difficulties, as in arthritis) along with increased bruising tendency in patients with chemotherapy and thrombocytopenia. DOACs have gained ground in clinical practice due to its oral route and its reliable anticoagulation without the need for lab testing. Because of these reasons, many clinicians are using DOACs off-label in cancer-associated VTE patients. Up until the Hokusai VTE Cancer study (edoxaban vs dalteparin), data on the use of DOACs in cancer patients have been limited to retrospective, meta-analysis, case reports and subgroup analysis of patients involved in the major trial involving DOACs. The Hokusai VTE Cancer study is the first randomized trial comparing a direct oral anticoagulant to a LMWH in cancer patients. It shows that edoxaban is non-inferior to dalteparin in the studied population, but it also showed that edoxaban is associated with higher rate of major bleeding namely in patients with gastrointestinal cancers. DOACs, with their various

mechanisms of action, have replaced warfarin in patients with nonvalvular atrial fibrillation and DVT/PE and are interchangeably used in the population of patients enrolled in their respective trials. Despite that edoxaban may represent DOACs in general, extrapolating the data from The Hokusai VTE Cancer study to generalize the use of other DOACs in cancer-associated VTE is rather premature and not advised, awaiting the data from currently running randomized trials involving the various other DOACs. The Hokusai VTE Cancer study may establish edoxaban as a new standard of care in the management of cancer-associated VTE, along with LMWHs, but it is also clear from the presented data that studies looking at subpopulation of cancer patients (examples include cancer patients being actively treated versus on no treatment, types of cancer- gastrointestinal versus others like genitourinary tumors, brain tumors, etc.) may be of more clinical value to clinicians who are trying to balance between treatment of thrombosis and risks of bleeding.

10. Five-year view

The various currently running trials involving various DOACs in cancer-associated VTE will likely follow edoxaban and show their efficacy when compared to LMWHs. This will increase the clinician's armamentarium of medications that can be used in cancer patients with VTE and thus will likely become the drug of choice replacing LMWHs. However, subpopulation analysis of these trials will likely help clinicians tailor their choices of treatment by identifying those with increased risk of bleeding with DOACs, as compared to LMWHs; thus, maximizing the efficiency of their treatment for the ultimate benefit of their patients. Moreover, in addition to discussing bleeding risks, evaluation of cost-effectiveness, which is a growing study element and likely to be evaluated for various DOACs, is likely to be an important material in the physician-patient discussions of treatment of choice. Such discussion would guide patients into choosing the treatment that would be more appropriate to them and that would ensure more compliance. In addition, antidotes for rivaroxaban, apixaban and edoxaban are expected to be available in the coming few years which will help clinicians and cancer patients be more comfortable

using DOACs even in situations of increased risk of bleeding, keeping in mind that these agents have not been found to improve clinical outcomes after bleeding.

11. Key Issues

- Cancer carries an increased risk of thrombosis and bleeding with the risks being dynamic during various treatment modalities and also affected by various types of cancer.
- Based on the CLOT trial, LMWH (dalteparin in the study) are currently the standards of care for cancer-associated VTE.
- DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) are increasingly being used in patients with VTE but studies in patients with cancer-associated VTE are limited.
- The Hokusai VTE Cancer study is the first randomized trial to show noninferiority of a DOAC (edoxaban in the study) when compared to a LMWH (dalteparin in this case).
- The Hokusai VTE Cancer study has also shown that there is increased risk of major bleeding associated with edoxaban, namely in patients with gastrointestinal cancer.
- Results from studies involving the other DOACs, with similar design to the Hokusai VTE Cancer study, are eagerly awaited.

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Declaration of interest

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***This review offers general guidelines for the treatment of venous thromboembolism in cancer patients. Major important studies are discussed including studies involving DOACs in cancer patients.**
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**This is a subgroup analysis of two large randomized trials of rivaroxaban versus warfarin, looking at cancer patients. This study revealed the efficacy of rivaroxaban in this subset of patients. This also likely paved the way for the currently running phase 3 trials comparing rivaroxaban to LMWHs in cancer patients with venous thromboembolism.

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***This article reviewed the basic pharmacology, clinical indications, and approach to the use of DOACs in cancer patients.**

Table-1: Major Clinical trials addressing the role of DOACs in the treatment of VTE

Study	Experimental arm Standard arm	(n)	VTE Recurrence Rate/ VTE-related deaths (%)	 HR (95% CI) P	Major bleedir %	 HR (95% CI) P
RE-COVER (17)	Dabigatran, at a fixed dose of 150 mg twice daily	1274	2.4	HR 1.10; 95% CI 0.65–1.84	1.6	0.82 (0.46-1.4
	Dose-adjusted warfarin therapy, after initial parenteral anticoagulation	1265	2.1		1.9	
RE-COVER-II (18)	Dabigatran, at a fixed dose of 150 mg twice daily	1280	2.3	HR: 1.08; 95% CI 0.64–1.80	1.2	0.69 (0.36-1.3
	Dose-adjusted warfarin therapy, after initial parenteral anticoagulation	1288	2.2		1.7	
EINSTEIN-DVT (21)	Rivaroxaban 15 mg bid ×3 weeks and then 20 mg od	1731	2.1	HR 0.68; 95% CI 0.44–1.04	0.8	0.65 (0.33-13(
	Enoxaparin 1 mg/kg bid SC/VKA	1718	3.0		1.2	0.21
EINSTEIN-PE (22)	Rivaroxaban 15 mg bid ×3 weeks and then 20 mg od	2419	2.1	HR 1.12; 95% CI 0.75–1.68	1.1	0.49 (0.31-0.7
	Enoxaparin 1 mg/kg bid SC/VKA	2413	1.8		2.2	0.003
AMPLIFY (25)	Apixaban 10 mg twice-daily for 7 days, followed by 5 mg twice-daily for 6 months	2691	2.3	0.84 0.60-1.18	0.6	0.31 (0.17-0.5
	Enoxaparin 1 mg/kg bid SC/VKA	2704	2.7		1.8	<0.001
HOKUSAI [27]	Enoxaparin or UFH for at least 5 days then Edoxaban 60 mg daily**	4118	3.2	0.89 0.70-1.13 <0.001	1.4	0.84 (0.59-1.2
	Enoxaparin or UFH for at least 5 days with Warfarin	4122	3.5		1.6	0.35

VTE: Venous thromboembolism; od: Once daily, bid: Twice daily; SC: Subcutaneous; VKA: Vitamin K Antagonist;

UFH: Unfractionated Heparin

*: RR, 0.31; 95% CI, 0.17–0.55; P=0.001 for superiority

**: 30 mg once daily in patients with a creatinine clearance of 30-50 ml per minute or a body weight of ≤60 kg or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors.

Features	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Dabigatran**
Treatment of DVT and PE	+	+	+	+
Target	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor
Half-life (Hours)	5-13	12	9-11	12-17
Onset of action (Hours)	2-4	3-4	1-3	2-3
Offset of action (Hours)	24-48	24-48	No data	
Clearance	Hepatobiliary: 66% Renal: 33%	Hepatobiliary: 73% Renal: 27%	Hepatobiliary: 50% Renal: 50%	Hepatobiliary: 20% Renal: 80%

Table-3: Major Clinical trials addressing the role of DOAC in the treatment of VTE in cancer patients

Study	Experimental arm Standard arm	(n)	VTE Recurrence Rate/ VTE-related deaths %	 HR (95% CI)	Major bleeding %	 HR (95% CI)	cli %
RE-COVER [31]*	Dabigatran, at a fixed dose of 150 mg bid	104	3.5	0.74 (0.20-2.7)	3.8	1.23 (0.28-5.5)	13
	Dose-adjusted warfarin therapy, after initial parenteral anticoagulation	107	4.7		3.0		9.0
EINSTEIN [32]	Rivaroxaban 15 mg bid ×3 weeks and then 20 mg od	354**	5.0	0.67 (0.35-1.30)	2.0	0.42 (0.18-0.99)	14
	Enoxaparin 1 mg/kg bid SC/VKA	301**	7.0		5.0		16
AMPLIFY [33]	Apixaban 10 mg twice-daily for 7 days, followed by 5 mg twice-daily for 6 months	88**	3.7	0.56 (0.13-2.37)	2.3	0.45 (0.08-2.46)	12
	Enoxaparin 1 mg/kg bid SC/VKA	81**	6.4		5.0		22
HOKUSAI [35]	Enoxaparin or UFH for at least 5 days then Edoxaban 60 mg daily****	378	3.7	0.53 0.28-1.00	2.6	0·80 (0·35-1·83)	12
	Enoxaparin or UFH for at least 5 days with Warfarin	393	7.1		3.3		18

VTE: Venous thromboembolism; od: Once daily, bid: Twice daily; SC: Subcutaneous; VKA: Vitamin K Antagonist; UFH: Unfractionated Heparin, (n): Number of patients

**: Data presented for the group of patients with cancer diagnosis at study entry, details in text.*

***: Patients with active cancer*

Table-4: Ongoing clinical trials addressing the role of DOACs in the treatment of VTE in cancer patients.

Study [Reference]	**ClinicalTrials.gov Identifier**	**DOAC**	**Comparator**	**Status**
Apixaban as Treatment of Venous Thrombosis in Patients With Cancer **The CAP Study** [37]	NCT02581176	Apixaban PO 10 mg bid for 1 week, then 5mg bid for 6 months, then 2.5 mg bid for as long as the treating physician finds it necessary.	None (Single arm)	Recruiti
A Phase III, Randomized, Open Label Study Evaluating the Safety of Apixaban in Subjects With Cancer Related Venous Thromboembolism [38]	NCT02585713	Apixaban 10 mg PO bid on days 1-7 then 5 mg bid on days 8-180.	Dalteparin 200 IU/kg/day SC od on days 1-30 then 150 IU/kg/day SC od on days 31-180.	Recruiti
Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer **CARAVAGGIO** [39]	NCT03045406	Apixaban 10 mg PO bid on days 1-7 then 5 mg bid on days 8-180	Dalteparin 200 IU/kg/day SC od on days 1-30 then 150 IU/kg/day SC od	Recruiti
A Randomized Phase II Study to Compare the Safety and Efficacy of Dalteparin vs. Rivaroxaban for Cancer associated Venous Thromboembolism **PRIORITY** [40]	NCT03139487	Rivaroxaban 15 mg PO bid for 3 weeks followed by 20mg od for 21 weeks	Dalteparin 200 IU/kg SC od for 4 weeks followed by 150 IU/kg od for 20 weeks	Recruiti
Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban **CASTA-DIVA** [41]	NCT02746185	Rivaroxaban PO, 15 mg bid for 3 weeks followed by 20 mg od for 9 weeks	Dalteparin 200 IU/kg SC od for one month followed by 150 IU/kg SC od for 2 months	Recruiti
Direct Oral Anticoagulants (DOACs) Versus LMWH +/- Warfarin for VTE in Cancer **CANVAS** [42]	NCT02744092	Rivaroxaban Apixaban Edoxaban Dabigatran	Dalteparin, Enoxaparin, Fondaparinux +/- Warfarin	Recruiti

Rivaroxaban in the Treatment of Venous Thromboembolism (VTE) in Cancer Patients **CONKO-011** [41]	NCT02583191	Rivaroxaban 15 mg bid for 21 days, followed by 20 mg od over a period of 3 months	Enoxaparin 1 mg/kg bid. Tinzaparin 175 IU/kg od. Dalteparin 200 IU/kg od	Recruiti
A Non-interventional Study on Xarelto for Treatment of Venous Thromboembolism (VTE) and Prevention of Recurrent VTE in Patients With Active Cancer **COSIMO** [43]	NCT02742623	Rivaroxaban Following 4 weeks therapy with LMWH and/or warfarin	Observational	Recruiti
A Prospective Study of Dabigatran Etexilate as Primary Treatment of Malignancy Associated Venous Thromboembolism [44]	NCT03240120	Tinzaparin 175 iu/kg daily for 6 days, then dabigatran 150mg bid from Day 6 onward till 6 months after underlying disease remission.	Observational	Not yet open

DOAC: Direct Oral Anticoagulants; VTE: Venous thromboembolism; PO: Oral, bid: Twice daily, od: Once daily; SC: Subcutaneous; LMWH: Low Molecular Weight Heparin; IU: International Unit