

## REVIEW

# Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants

C. Ay<sup>1,2\*</sup>, J. Beyer-Westendorf<sup>3,4</sup> & I. Pabinger<sup>1</sup>

<sup>1</sup>Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria; <sup>2</sup>I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia; <sup>3</sup>Thrombosis Research Unit, Division of Haematology, Department of Medicine I, University Hospital “Carl Gustav Carus” Dresden, Dresden, Germany; <sup>4</sup>Department of Haematology, King’s College London, London, UK

\*Correspondence to: Dr Cihan Ay, Department of Medicine I, Clinical Division of Haematology and Haemostaseology, Medical University of Vienna, Waehinger Guertel 18-20, A-1090 Vienna, Austria. Tel: +43-1-40400-44100; Fax: +43-1-40400-40300; E-mail: cihan.ay@meduniwien.ac.at

Anticoagulation for cancer-associated venous thromboembolism (VTE) can be challenging due to complications—including bleeding and potential drug–drug interactions with chemotherapy—associated with vitamin K antagonists and inconvenience of low-molecular-weight heparin (LMWH). Direct oral anticoagulants (DOACs) could partially overcome these issues, but until recently there were no large clinical trials assessing their efficacy and safety in cancer patients. This review summarizes clinical treatment guidelines, prior clinical and real-world evidence for anticoagulant choice, recent clinical trials assessing DOACs for cancer-associated VTE (i.e. Hokusai-VTE Cancer, SELECT-D, CARAVAGGIO, and ADAM VTE), and special considerations for DOAC use. Based on established data, clinical guidelines recommend patients with cancer-associated VTE receive LMWH treatment of at least 3–6 months. Nevertheless, LMWH is underused and associated with poor compliance and persistence in these patients relative to oral anticoagulants. Clinical data supporting DOAC use in cancer patients are becoming available. In Hokusai-VTE Cancer, edoxaban was noninferior to dalteparin for the composite of recurrent VTE and major bleeding (12.8% versus 13.5%), with numerically lower recurrent VTE (7.9% versus 11.3%) and significantly higher major bleeding (6.9% versus 4.0%); only patients with gastrointestinal cancer had significantly higher risk of bleeding with edoxaban. In SELECT-D, rivaroxaban had numerically lower VTE recurrence (4% versus 11%), comparable major bleeding (6% versus 4%), and numerically higher clinically relevant nonmajor bleeding (13% versus 4%) versus dalteparin. Most bleeding events were gastrointestinal or urologic; patients with esophageal/gastroesophageal cancer had higher rates of major bleeding with rivaroxaban (36% versus 11%). For comparison of apixaban versus dalteparin, CARAVAGGIO is ongoing, and preliminary results from ADAM VTE are favorable. This review concludes that DOACs appear to be reasonable alternatives to LMWH for treatment of cancer-associated VTE. In patients with gastrointestinal cancer, DOAC use should be considered on a case-by-case basis with consideration of the relative risks and benefits.

**Key words:** venous thromboembolism, cancer, treatment, direct oral anticoagulants

## Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant concern for patients with cancer. For example, the occurrence of cancer-associated VTE is a significant predictor of death within 1 year of cancer diagnosis [1]. In addition, VTE is one of the leading causes of death in cancer patients receiving outpatient chemotherapy [2], and a VTE diagnosis can delay or interrupt initiation of adjuvant chemotherapy [3].

The risk for cancer-associated VTE depends on cancer type and is generally higher in patients with metastatic disease; an international meta-analysis of VTE in patients with cancer found an annual incidence between 0.5% and 20% depending on cancer type and other risk factors [4]. Several validated risk scoring models exist for cancer-associated VTE, which include factors based on clinical characteristics (e.g. tumor type and body mass index), laboratory parameters (e.g. hemoglobin levels and thrombocyte counts), and biomarkers (e.g. soluble P-selectin and D-dimer) [5–8].

Treatment of VTE in patients with cancer can be challenging due to complications including increased risk of bleeding and potential drug–drug interactions with chemotherapy. Vitamin K antagonists (VKAs) after initial heparin treatment were a recommended option for long-term oral treatment of VTE in patients without cancer [9]. However, VKAs are not recommended for cancer-associated VTE. Relative to patients without cancer, patients with cancer are at threefold to fourfold higher risk for VTE recurrence even with VKA treatment and are up to a sixfold higher risk for anticoagulant-associated bleeding [10, 11]. Furthermore, potential complications of cancer treatment such as chemotherapy-induced vomiting and drug–drug interactions between VKAs and anticancer medications can interfere with oral anticoagulants [12, 13]. Low-molecular-weight heparin (LMWH) treatment is associated with similar or lower rates of VTE recurrence and bleeding relative to VKAs in patients with cancer-associated VTE, does not rely on gastrointestinal absorption, and interacts minimally with chemotherapy agents [12, 14, 15]. Therefore, LMWH is recommended by clinical guidelines and other practice guidance as first-line treatment of short- and long-term management of cancer-associated VTE [12, 13, 16–19].

Direct oral anticoagulants (DOACs), including direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban), have advantages relative to VKAs including fixed dose regimen, predictable pharmacology and anticoagulation, and no need for regular laboratory monitoring. In addition, unlike LMWH, DOACs are orally dosed and do not require long-term subcutaneous injections, which can act as a barrier to regular LMWH treatment [20]. As a class, DOACs have similar efficacy as VKAs for treatment of acute VTE, but are associated with less major bleeding [21]. Until recently, there was limited clinical data from randomized clinical trials on efficacy and safety of DOACs versus LMWH for treatment of cancer-associated VTE. However, newly available evidence suggests a role for DOACs for VTE treatment in many patients with cancer. This review will discuss the current standard of treatment and the existing evidence, newly published and ongoing studies, and possible issues regarding DOACs for treatment of VTE in patients with cancer.

### Clinical guideline recommendations

The clinical guideline recommendations for LMWH for long-term treatment of cancer-associated VTE are largely based on four clinical trials [14, 15, 22, 23]. The largest of these, CLOT, found a significantly lower rate of VTE recurrence and numerically lower rate of any bleeding in patients treated long-term with dalteparin versus VKAs [14]. The most recently published study, CATCH, enrolled a lower-risk population with lower-than-expected VTE recurrence and found a numerically lower VTE recurrence rate compared with CLOT [15]. CATCH reported a similar rate of major bleeding events in patients treated with tinzaparin versus warfarin, but a significantly lower rate of clinically relevant nonmajor (CRNM) bleeding [15].

Despite clinical consensus, LMWH treatment of cancer-associated VTE is underused relative to clinical guideline recommendations [24–27]. This is attributed in part to disadvantages related to patient preference, convenience, and cost [20], which may also contribute to poor treatment persistence. Despite high

risk for VTE recurrence, patients with cancer-associated VTE have higher anticoagulation interruption and discontinuation rates relative to patients with other VTE risk factors [28], and they are more likely to switch anticoagulant agents and less likely to persist on therapy when treated with LMWH versus warfarin or rivaroxaban [25]. There is thus a need for oral anticoagulant options with demonstrated efficacy and safety comparable to LMWH in patients with cancer-associated VTE.

### DOACs for treatment of cancer-associated VTE

Due to insufficient data at the time they were drafted, clinical guidelines published before 2018 include few recommendations on DOACs for treatment of cancer-associated VTE [12, 16, 17, 19]. Until recently, there was only mid-level evidence available to inform the use of DOACs in patients with cancer-associated VTE, derived primarily from secondary analyses of pivotal phase III clinical trial data for each of the DOACs (Table 1) [29–32]. These studies enrolled limited numbers of patients with cancer, and some excluded patients with active cancer for whom long-term LMWH treatment was planned [31, 32], as well as patients with intracranial neoplasia [29] or life expectancy <6 months [29, 31]. Approximately 6% of patients in phase III trials of DOACs versus VKA for VTE treatment had active cancer, although definitions of active cancer differed substantially among the studies (Table 1) [29–33]. Nevertheless, all four studies found comparable rates of VTE recurrence and similar or lower rates of bleeding events in patients with active cancer treated with DOACs versus VKAs (Table 1) [29–32]. Where cause of major bleeding events was reported, the majority among all patients were considered cancer related [29, 30]. A 2015 network meta-analysis of randomized, controlled trials of LMWH, VKAs, and DOACs for treatment of cancer-associated VTE—including these four studies as well six studies comparing LMWH versus VKAs—suggested the efficacy and safety of DOACs were noninferior to VKAs and possibly comparable with LMWH [34].

### Real-world data and observational studies

Despite guideline recommendations to use LMWH in patients with cancer-associated VTE, emerging real-world data show that DOACs have been widely used in patients with active cancer even before evidence from randomized trials or guideline recommendations supported this practice. Results from real-world studies offer important insights from clinical practice, but they provide lower-level evidence relative to randomized controlled trials and must therefore be interpreted cautiously due to potential patient and treatment selection biases. Although patients with active cancer were more likely to be treated with parenteral anticoagulant relative to patients without cancer in the GARFIELD-VTE registry, 22.8% of patients with cancer received DOACs [35]. A large retrospective study of patients with cancer who developed VTE and received anticoagulants identified 707 patients treated with rivaroxaban versus 1061 treated with warfarin and 660 treated with LMWH [36]. After adjusting for baseline characteristics between treatment cohorts, overall VTE recurrence was significantly lower by 28% in patients treated with rivaroxaban versus

**Table 1. Results of subanalyses of patients with cancer-associated VTE in pivotal phase III DOAC trials**

	RE-COVER I/II [29]	EINSTEIN-DVT/PE [30]	AMPLIFY [31]	Hokusai-VTE [32]	
Study design					
DOAC	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	
Comparator	Warfarin	VKA	Warfarin	Warfarin	
Follow-up time	6 months	3–12 months	6 months	3–12 months	
Noncancer exclusion criteria					
Life expectancy	<6 months	<3 months	<6 months	<3 months	
Long-term LMWH planned	NS	NS	Yes	Yes	
Definition of active cancer				<i>Prespecified</i>	<i>Post hoc</i>
Diagnosis relative to randomization	≤5 years	≤6 months	≤6 months	NS	Measurable
Nonmelanoma skin cancer excluded	Yes	No	No	NS	Yes
Other cancers excluded	Intracranial	NS	NS	NS	NS
Active cancer at randomization, <i>n</i>				<i>Prespecified</i>	<i>Post hoc</i>
DOAC	114	258	88	109	85
Comparator	107	204	81	99	77
Outcomes <sup>a</sup>				<i>Prespecified</i>	<i>Post hoc</i>
Primary efficacy end point	Recurrent VTE	Recurrent VTE	Recurrent VTE	Recurrent VTE	
Rate, DOAC versus VKA	3.5% versus 4.7%	2% versus 4%	3.7% versus 6.4%	4% versus 7%	2% versus 9%
HR (95% CI)	0.74 (0.20–2.7)	0.62 (0.21–1.79)	0.56 (0.13–2.37)	0.55 (0.16–1.85)	0.30 (0.06–1.51)
Principal safety end point	CR bleeding <sup>b</sup>	CR bleeding	Major bleeding	CR bleeding	
Rate, DOAC versus VKA	13% versus 9.0%	12% versus 13%	2.3% versus 5.0%	18% versus 25%	19% versus 26%
HR (95% CI)	1.48 (0.64–3.4)	0.82 (0.48–1.38)	0.45 (0.08–2.46) <sup>c</sup>	0.72 (0.40–1.30)	0.66 (0.34–1.27)

<sup>a</sup>Outcomes shown for patients with active cancer at baseline.

<sup>b</sup>Prespecified safety outcome but not specified as principal safety analysis.

<sup>c</sup>Relative risk (95% CI).

CI, confidence interval; CR, clinically relevant; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HR, hazard ratio; LMWH, low-molecular-weight heparin; NS, not specified; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

LMWH and by 26% in patients receiving rivaroxaban relative to warfarin, and major bleeding rates were similar in patients taking rivaroxaban relative to LMWH or warfarin [36]. A single-center retrospective cohort study found no significant difference in recurrent VTE or bleeding between 190 DOAC-treated patients versus 290 LMWH-treated patients [37], and comparison of 98 prospective registry patients taking rivaroxaban for cancer-associated VTE versus 168 contemporary patients treated with enoxaparin found no difference in VTE recurrence or bleeding rates [38]. Smaller retrospective studies found DOACs generally at least as safe and effective as LMWH in patients with cancer [39–44]. Meta-analysis of observational studies is difficult due to population and end point heterogeneity, but a recent systematic review of DOACs for treatment of cancer-associated thrombosis reported lower rates of recurrent VTE in patients treated with DOACs versus LMWH in all but one observational study and higher rates of major bleeding only in two studies restricted to patients with gastrointestinal or gynecological cancers [45].

### Clinical trials of DOACs versus LMWH for treatment of cancer-associated VTE

New data from two recent randomized, open-label clinical trials with blinded end point adjudication provide the highest level of evidence to date for the role of oral factor Xa inhibitors in

treatment of cancer-associated VTE [46, 47]. Hokusai-VTE Cancer evaluated edoxaban versus dalteparin treatment [46], and Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism (SELECT-D) compared rivaroxaban versus dalteparin treatment [47]. A similar prospective, randomized, open-label with blind end point evaluation study of apixaban versus dalteparin treatment, Apixaban for the Treatment of Venous Thromboembolism in Patients with Cancer (CARAVAGGIO; clinicaltrials.gov NCT03045406), is recruiting [48, 49]. Although these studies are more similar than the secondary analyses of patients with cancer in the pivotal phase III trials of DOACs for VTE treatment, they have design differences that may confound comparison of the results (Table 2). All studies include patients with cancer other than basal cell or squamous cell skin cancer and Eastern Cooperative Oncology Group performance status ≤2 [46, 47, 49]. All three studies focus mainly on patients with active cancer, defined as cancer diagnosed or treated ≤6 months before randomization, recurrent or metastatic cancer—including locally or regionally advanced cancer in Hokusai-VTE Cancer and CARAVAGGIO, respectively—or hematologic cancer not in complete remission [46, 47]. Hokusai-VTE Cancer also includes patients with cancer diagnosed within the previous two years and objectively confirmed, and CARAVAGGIO includes patients with history of cancer <2 years before enrollment and excludes patients with primary brain tumors, intracerebral metastases, or acute leukemia [46, 49].

**Table 2. Comparison of Hokusai-VTE cancer, SELECT-D, and CARAVAGGIO study design and patient population**

	<b>Hokusai-VTE cancer [46]</b>	<b>SELECT-D [47]</b>	<b>CARAVAGGIO [49]</b>
<b>Design</b>	Randomized, open-label with blinded end point adjudication	Randomized, open-label with blinded end point adjudication	Randomized, open-label with blinded end point adjudication
<b>Stratification criteria</b>	Edoxaban dose adjustment Bleeding risk	Cancer stage Symptomatic VTE versus incidental PE Clotting risk by tumor type Platelet count	Active cancer versus cancer history Symptomatic versus incidental VTE
<b>Enrollment, N</b>	1050	406	1168 <sup>a</sup>
<b>Treatments</b>	Edoxaban 60/30 mg PO o.i.d. <sup>b</sup> versus dalteparin 200/150 IU/kg SC o.i.d. <sup>c</sup>	Rivaroxaban 15 mg PO b.i.d./20 mg PO o.i.d. <sup>d</sup> versus dalteparin 200/150 IU/kg SC o.i.d. <sup>e</sup>	Apixaban 10/5 mg <sup>e</sup> PO b.i.d. versus dalteparin 200/150 IU/kg SC o.i.d. <sup>c</sup>
<b>Required LMWH lead-in for DOAC-treated patients</b>	Therapeutic-dose LMWH for ≥5 days	None	None
<b>Duration</b>	6–12 months	6 months	6 months
<b>Qualifying VTE diagnosis</b>	Acute symptomatic or incidentally detected DVT of the popliteal, femoral, or iliac vein or inferior vena cava; acute, symptomatic PE confirmed by imaging; incidentally detected PE of segmental or more proximal pulmonary arteries	Symptomatic lower-extremity proximal DVT, symptomatic PE, or incidental PE	Newly diagnosed, objectively confirmed, symptomatic or incidental <sup>f</sup> proximal lower-limb DVT of the popliteal or more proximal vein, symptomatic PE, or incidental <sup>f</sup> PE in a segmental or more proximal pulmonary artery
<b>Qualifying cancer diagnosis</b>	Active cancer Cancer diagnosed ≤2 years before randomization and objectively confirmed	Active cancer	Active cancer History of confirmed cancer diagnosed ≤2 years before randomization and not fulfilling criteria for active cancer <sup>f</sup>
<b>Cancers excluded</b>	Basal-cell skin cancer Squamous-cell skin cancer	Basal-cell skin carcinoma Squamous-cell carcinoma Esophageal or gastroesophageal cancer <sup>g</sup>	Basal-cell skin carcinoma Squamous-cell skin carcinoma Primary brain tumor Intracerebral metastasis Acute leukemia
<b>Other exclusions</b>	Certain P-gp inhibitors	Strong inhibitors or inducers of CYP3A4 or P-gp	Strong inhibitors or inducers of CYP3A4 and P-gp
<b>Concomitant medication</b>	No	Yes	No
<b>Prior VTE</b>	No	Yes	Yes
<b>High bleeding risk</b>	Composite of recurrent VTE or major bleeding	Recurrent VTE	Recurrent VTE
<b>Primary outcome</b>			Major bleeding
<b>Recurrent VTE definition</b>	Symptomatic or unsuspected recurrent DVT of the leg, including new DVT or increased thrombus diameter confirmed by imaging; symptomatic new or recurrent PE of segmental or proximal pulmonary arteries; unsuspected new PE involving segmental or more proximal pulmonary arteries; fatal PE; or death possibly due to PE	Recurrent proximal lower-extremity DVT, including new DVT or increased thrombus diameter, confirmed by imaging; venous thrombosis at other sites; symptomatic or incidental PE confirmed by imaging; fatal PE; or death possibly due to PE	Objectively confirmed, symptomatic or incidental proximal lower-limb DVT; symptomatic upper-limb DVT; symptomatic, incidental, or fatal PE; or sudden and unexplained death most probably due to PE

*Continued*

Table 2. Continued

	Hokusai-VTE cancer [46]	SELECT-D [47]	CARAVAGGIO [49]
Key secondary outcomes	Recurrent VTE	Major and CRNM bleeding	Symptomatic recurrent VTE
Efficacy	Major bleeding CRNM bleeding		Quality of life
Safety			CRNM bleeding Major and CRNM bleeding Treatment discontinuation
<p><sup>a</sup>Planned.</p> <p><sup>b</sup>Adjusted to 30 mg/day in patients with creatinine clearance 30–50 ml/min, body weight ≤60 kg, or receiving concomitant strong P-gp inhibitors.</p> <p><sup>c</sup>200 IU/kg for 30 days followed by 150 IU/kg until end of treatment.</p> <p><sup>d</sup>1.5 mg PO b.i.d. for 3 weeks followed by 20 mg PO o.i.d. until end of treatment.</p> <p><sup>e</sup>10 mg b.i.d. for 7 days followed by 5 mg b.i.d. until end of treatment.</p> <p><sup>f</sup>Enrollment of patients with incidental VTE or history of cancer capped at 20% of overall study population each.</p> <p><sup>g</sup>Excluded mid-study after data and safety monitoring committee review.</p> <p>b.i.d., twice daily; CYP3A4, cytochrome P450 3A4; CRNM, clinically relevant nonmajor; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; IU, international units; LMWH, low-molecular-weight heparin; o.i.d., once daily; PE, pulmonary embolism; P-gp, P-glycoprotein; PO, orally; SC, subcutaneous; VTE, venous thromboembolism.</p>			

Patients with symptomatic lower-limb DVT or symptomatic or unsuspected PE are included in all studies. Patients with incidentally detected lower-limb DVT are included in Hokusai-VTE Cancer and CARAVAGGIO, but not SELECT-D. Hokusai-VTE Cancer and CARAVAGGIO include patients with incidental PE only when segmental or more proximal pulmonary arteries are affected [46, 47, 49]. Patients considered at high risk for bleeding are also excluded from SELECT-D and CARAVAGGIO but not Hokusai-VTE Cancer [46, 47, 49].

The dalteparin treatment protocol (200 IU/kg/day for 30 days and 150 IU/kg/day thereafter), derived from the CLOT trial, is identical in all three studies [14, 46, 47, 49]. The primary outcome is recurrent VTE in SELECT-D and CARAVAGGIO and a composite of recurrent VTE and major bleeding in Hokusai-VTE Cancer [46, 47, 49]. Recurrent VTE includes visceral or upper limb thrombosis in SELECT-D and upper limb DVT in CARAVAGGIO; Hokusai-VTE Cancer does not explicitly include upper limb DVT and excludes unsuspected subsegmental pulmonary artery PE [46, 47, 49]. Major bleeding is the primary safety outcome in CARAVAGGIO and a secondary outcome in SELECT-D [47, 49]. All three studies use the International Society for Thrombosis and Haemostasis (ISTH) definition of major bleeding (i.e. overt bleeding associated with a ≥2 g/dl decrease in hemoglobin level, leading to transfusion of ≥2 units of blood, occurring in a critical site, and/or contributing to death) [50] and define CRNM bleeding by similar criteria [46, 47, 49]. SELECT-D assessed outcomes after ≤6 months and Hokusai-VTE Cancer after ≤12 months of treatment; CARAVAGGIO will assess outcomes after ≤6 months of treatment [46, 47, 49].

Several other ongoing clinical trials are assessing DOACs versus LMWH for treatment of cancer-associated VTE. The investigator-initiated, randomized, open-label Apixaban and Dalteparin in Active Malignancy-associated VTE trial (ADAM VTE; NCT02585713) compares the rate of major bleeding in patients with cancer and acute VTE treated with apixaban versus dalteparin for 6 months. In ADAM VTE, the rate of recurrent VTE or arterial thromboembolism is the secondary efficacy outcome [51]. Similar to SELECT-D, CONKO-011 (NCT02583191) is evaluating rivaroxaban versus dalteparin but with patient-reported treatment satisfaction as the primary outcome [52]. The Comparing Oral and Injectable Blood Thinners to Prevent and Treat Blood Clots in Patients with Cancer (CANVAS; NCT02744092) trial randomizes patients with cancer and VTE ≤30 days before randomization to treatment with a DOAC (edoxaban, apixaban, rivaroxaban, or dabigatran) versus LMWH with or without transition to warfarin for 6 months [53]. Within each treatment arm, patients may choose the specific drug based on side effects and practical considerations [53]. The primary outcome in CANVAS is VTE recurrence; secondary outcomes include major bleeding, health-related quality of life, and burden of anticoagulant therapy [53].

### Results from Hokusai-VTE Cancer and SELECT-D

Hokusai-VTE Cancer enrolled 1050 patients, of whom 11% had hematological malignancies and 89% had solid tumors [46]. The most frequent tumor types were colorectal (15.9% versus 15.1%),



lung (14.8% versus 14.3%), genitourinary (12.5% versus 13.5%), and breast (12.3% versus 11.5%) in patients receiving edoxaban versus dalteparin; 6.3% of edoxaban-treated patients versus 4.0% of dalteparin-treated patients had upper gastrointestinal cancer [46]. Median treatment duration was numerically longer for edoxaban (211 days) versus dalteparin (184 days), and 38.3% of patients receiving edoxaban versus 29.4% receiving dalteparin completed study treatment [46]. Patients taking edoxaban versus dalteparin had relatively similar rates of treatment discontinuation due to death (16.5% versus 19.1%) and clinical outcome or adverse event (15.1% versus 11.8%) [46]. However, the rate of treatment discontinuation due to patient dissatisfaction with dosing inconvenience was numerically higher for dalteparin (14.9%) relative to edoxaban (4.0%) [46]. Edoxaban was statistically noninferior to dalteparin; the composite primary outcome of recurrent VTE or major bleeding occurred in 12.8% of patients receiving edoxaban versus 13.5% of patients receiving dalteparin [46]. Edoxaban was associated with a numerical 3.4% lower absolute rate of recurrent VTE (7.9% versus 11.3%) and a significant 2.9% higher absolute rate of major bleeding (6.9% versus 4.0%) compared with dalteparin [46]. Death related to VTE or bleeding occurred in six patients in each treatment group [46]. Event-free survival and death from any cause were similar between edoxaban and dalteparin (55.0% versus 56.5% and 39.5% versus 36.6%, respectively) [46]. In subgroup analyses, only patients with gastrointestinal cancer were at a significantly increased risk of bleeding with edoxaban treatment relative to dalteparin [46].

A secondary analysis of Hokusai-VTE Cancer focused on the sites, clinical presentation, clinical course and outcome, and the tumor types associated with bleeding events in more detail [54]. This analysis confirmed that there were no fatal bleeds with edoxaban treatment, and two fatal bleeds with dalteparin (one patient with metastatic breast cancer had fatal subdural hematoma after a fall; one patient with metastatic skin melanoma had fatal lower gastrointestinal bleeding) [54]. Overall, severe bleeding (bleeding events that presented as medical emergencies or were almost immediately fatal) was reported in 1.9% of edoxaban patients and 2.1% of dalteparin patients [54]. Among patients with gastrointestinal cancer, the clinical presentation of bleeding was severe in 3.0% versus 2.1% with edoxaban and dalteparin treatment, respectively [54]. Furthermore, in patients with gastrointestinal cancers, the clinical presentation was upper gastrointestinal bleeding in the majority (71.4%) of major bleeding events in the edoxaban group [54].

SELECT-D was a smaller study than Hokusai-VTE Cancer, with 406 patients enrolled [47]. The most common primary cancer types were colorectal (27% versus 23%), lung (11% versus 12%), and breast (10% each) in patients receiving rivaroxaban versus dalteparin; hematologic cancers and genitourinary cancers were reported as individual tumor types rather than categories [47]. An interim safety review of the first 220 patients found a difference in major bleeding between patients with esophageal or gastroesophageal cancer receiving rivaroxaban versus dalteparin, and such patients were subsequently excluded from enrollment; in the final analysis, 5% of rivaroxaban-treated patients and 9% of dalteparin-treated patients had esophageal or gastroesophageal tumors [47]. Median treatment duration was similar between rivaroxaban and dalteparin (5.9 versus 5.8 months) [47]. Patients receiving rivaroxaban versus dalteparin most often discontinued

study treatment because of death (rivaroxaban, 28/203; dalteparin, 33/203), outcome or adverse event (rivaroxaban, 35/203; dalteparin, 22/203), and patient decision (rivaroxaban, 7/203; dalteparin, 10/203); the most common reason for study withdrawal was patient choice (rivaroxaban, 11/203; dalteparin, 19/203) [47]. Patients receiving rivaroxaban had a numerically lower rate of VTE recurrence (4% versus 11%), comparable rate of major bleeding (6% versus 4%), and numerically higher rate of CRNM bleeding (13% versus 4%) relative to patients receiving dalteparin [47]. Most major bleeding events were gastrointestinal, and patients with esophageal or gastroesophageal cancer experienced major bleeding numerically more frequently when treated with rivaroxaban relative to dalteparin (36% versus 11%) [47]. Most CRNM bleeding events were gastrointestinal or urologic [47].

Meta-analysis of 6-month outcomes in Hokusai-VTE Cancer and SELECT-D reported lower incidence of recurrent VTE [relative risk (RR): 0.65; 95% confidence interval (CI): 0.42–1.01], higher incidence of major bleeding (RR: 1.74; 95% CI: 1.05–2.88), and CRNM bleeding (RR: 2.31; 95% CI: 0.85–6.28), and no difference in mortality (RR: 1.03; 95% CI: 0.85–1.26) in patients treated with edoxaban or rivaroxaban versus dalteparin [45]. Mortality was also similar between patients with cancer and VTE treated with DOACs versus LMWH in the individual studies. Hokusai-VTE Cancer reported death rates of 15.3% versus 13.5% after 3 months, 26.8% versus 24.2% after 6 months, and 39.5% versus 36.6% after 12 months in patients treated with edoxaban versus dalteparin, respectively; 181/206 deaths in patients taking edoxaban and 172/192 deaths in patients receiving dalteparin were considered cancer related [46]. Overall 6-month survival rates in SELECT-D were comparable between patients taking rivaroxaban (75%) versus dalteparin (70%); causes of death were not reported [47].

Preliminary results from ADAM VTE were presented at the 2018 American Society of Hematology meeting. Patients treated with apixaban ( $n=145$ ) had similar, very low rates of major bleeding, a significantly lower rate of VTE recurrence, and similar rates of major + CRNM bleeding and mortality relative to dalteparin-treated patients ( $n=142$ ) [51]. Notably, ADAM VTE was a smaller study relative to Hokusai-VTE Cancer or SELECT-D, outcome event rates differed between the published abstract and the oral presentation, and certain important tumor types (colorectal, lung, and genitourinary) were unevenly distributed between treatment arms. Consequently, the role of apixaban in treatment of cancer-associated VTE will remain uncertain until further trials report apixaban results in this setting.

## Special considerations for use of DOACs in the treatment of cancer-associated VTE

### Practical considerations

Although DOAC treatment is associated with lower rates of VTE recurrence and comparable rates of major bleeding relative to LMWH in patients with cancer, particularly nongastrointestinal cancer, practical considerations may limit DOAC use. Unlike parenteral LMWH, oral anticoagulants including DOACs are subject to interference from chemotherapy-induced nausea and vomiting; therefore, LMWH may be preferable in patients with

frequent vomiting [12]. The DOACs require careful dosing in patients with renal impairment, and drug labeling provides little support for use of DOACs to treat VTE in patients with severe renal impairment [55–58]. Similar concerns apply to LMWH use in patients with severe renal impairment, and unfractionated heparin or VKAs are preferred in this population [12, 19, 59]. Caution is also required in patients with thrombocytopenia; current clinical guideline recommendations and practice guidance suggestions include standard-dose LMWH treatment in patients with platelet counts  $>50\ 000/\mu\text{l}$  and no evidence of bleeding, and case-by-case decisions based on individual risk/benefit considerations for patients with platelet counts  $<50\ 000/\mu\text{l}$  [12, 60]. The 2018 ISTH guidance suggests withholding anticoagulation in patients with platelet counts  $<25\ 000/\mu\text{l}$  who are at lower risk for recurrent VTE and considering platelet transfusion to maintain platelet counts above  $40\ 000\text{--}50\ 000/\mu\text{l}$  in patients with thrombocytopenia and high risk for VTE recurrence [60].

Another concern in DOAC use in patients with cancer is drug–drug interactions with anticancer agents [12]. Apixaban, rivaroxaban, and edoxaban are substrates of cytochrome 450 3A4 (CYP3A4) to varying degrees—edoxaban is minimally metabolized by CYP3A4—and of P-glycoprotein (P-gp), and the prodrug dabigatran etexilate is also a P-gp substrate [61, 62]. Strong CYP3A4 and P-gp inhibitors significantly increase DOAC plasma levels, while strong CYP3A4 and P-gp inducers significantly decrease plasma DOAC levels [61, 62]. The importance of potential interactions of anticancer agents with DOACs via CYP3A4 or P-gp have been comprehensively reviewed elsewhere [61–63]. In brief, anticancer drug classes with potential class-wide interactions with DOACs include antimetabolic microtubule inhibitors, most tyrosine kinase inhibitors, and most immunomodulating agents including glucocorticoids [62]; cyclosporine is known to increase plasma edoxaban exposure [64]. There are also potential interactions between DOACs and individual drugs among the topoisomerase inhibitors, anthracyclines, alkylating agents, and hormonal agents [62]. However, antimetabolites, platinum-based agents, intercalating agents, and monoclonal antibodies have minimal potential for drug–drug interactions with DOACs [62].

Although SELECT-D and CARAVAGGIO exclude patients taking any strong inducer or inhibitor of CYP3A4 or P-gp, Hokusai-VTE Cancer excludes only patients using certain potent P-gp-inhibiting drugs, with dose adjustment to edoxaban 30 mg once daily for patients taking other strong P-gp inhibitors [46–48]. Patients in Hokusai-VTE Cancer continued treatment with several anticancer medications with potential interactions with edoxaban, including taxanes (7.7% of edoxaban-treated patients), topoisomerase inhibitors (5.7%), kinase inhibitors (3.4%), vinca alkaloids (3.1%), and immunomodulating agents (3.1%) [46]. The comparable safety and efficacy of edoxaban versus dalteparin in Hokusai-VTE Cancer patients with nongastrointestinal cancers suggests that drug–drug interactions between DOACs and anticancer agents are clinically manageable. Ongoing studies evaluating interactions of apixaban with anticancer agents (NCT03083782 and NCT02749617) [65, 66] should provide additional data to guide dose adjustments.

### Special populations

Certain populations of patients with cancer have increased risk of VTE recurrence and/or bleeding and require special consideration

during anticoagulant treatment of cancer-associated VTE. Patients with brain tumors are at high risk for recurrent VTE and anticoagulant-associated intracranial hemorrhage (ICH), although the bleeding risk is not considered a contraindication to anticoagulation [59]. Patients with brain tumors were included in both Hokusai-VTE Cancer (reported as ‘other’) and SELECT-D ( $n=3$ ), but not in sufficient numbers to assess the RR of ICH during treatment with DOACs versus LMWH [46, 47]. Patients with multiple myeloma have high rates of VTE due to disease- and treatment-specific risk factors [18], but neither Hokusai-VTE Cancer nor SELECT-D enrolled large numbers of such patients [46, 47]. Finally, patients with gastrointestinal cancer experienced higher rates of gastrointestinal bleeding during treatment with edoxaban or rivaroxaban relative to LMWH [46, 47]. Based on available evidence and as reflected in the ISTH Scientific and Standardization Committee (SSC) 2018 guidance on the role of DOACs in treatment of cancer-associated VTE, patients with gastrointestinal cancer and VTE should not receive DOACs when other anticoagulant options are available [67]. Limited data are available on treatment of cancer-associated VTE in patients with additional noncancer risk factors for anticoagulant-associated bleeding, such as elderly patients and patients with renal impairment, but extrapolation from studies in patients without cancer suggests additional monitoring may be appropriate during use of any anticoagulant agent [59].

### Discussion

The results of Hokusai-VTE Cancer and SELECT-D show that edoxaban and rivaroxaban are equally or more effective relative to dalteparin for prevention of VTE recurrence but confer higher risk for major bleeding in patients with cancer, especially gastrointestinal cancer [45]. The association between gastrointestinal cancer and upper gastrointestinal bleeding in patients taking edoxaban might be due to high concentrations of edoxaban in the gastrointestinal lumen exacerbating bleeding directly from the tumor or from gastrointestinal mucosa damaged by chemotherapy targeting gastrointestinal tumors [54]. In light of these data, the ISTH SSC 2018 guidance suggests edoxaban or rivaroxaban for cancer patients with an acute diagnosis of VTE, low risk of bleeding, and no drug–drug interactions with current systemic therapy, after shared decision-making with patients to balance potential reduction in VTE recurrence versus higher bleeding rates [67]. The 2018 National Comprehensive Cancer Network guidance prefers LMWH monotherapy, but suggests DOAC use in patients for whom long-term LMWH therapy is not an option; they note that further investigation in cancer patients is needed for apixaban and dabigatran [68].

The commonalities between the results of Hokusai-VTE Cancer and SELECT-D trial results predicted similar trends for apixaban, but bleeding rates in ADAM VTE were similar between patients treated with apixaban versus dalteparin [51]. However, although the dalteparin treatment protocol was identical, the rate of major bleeding in dalteparin-treated patients was lower in ADAM VTE relative to Hokusai-VTE Cancer and SELECT-D [46, 47, 51], suggesting inter-study differences in patient selection or management. This is especially important because availability of results from Hokusai-VTE, SELECT-D, and ADAM VTE may caution CARAVAGGIO investigators not to include patients with certain cancers—such as colorectal cancer, associated with excess gastrointestinal bleeding

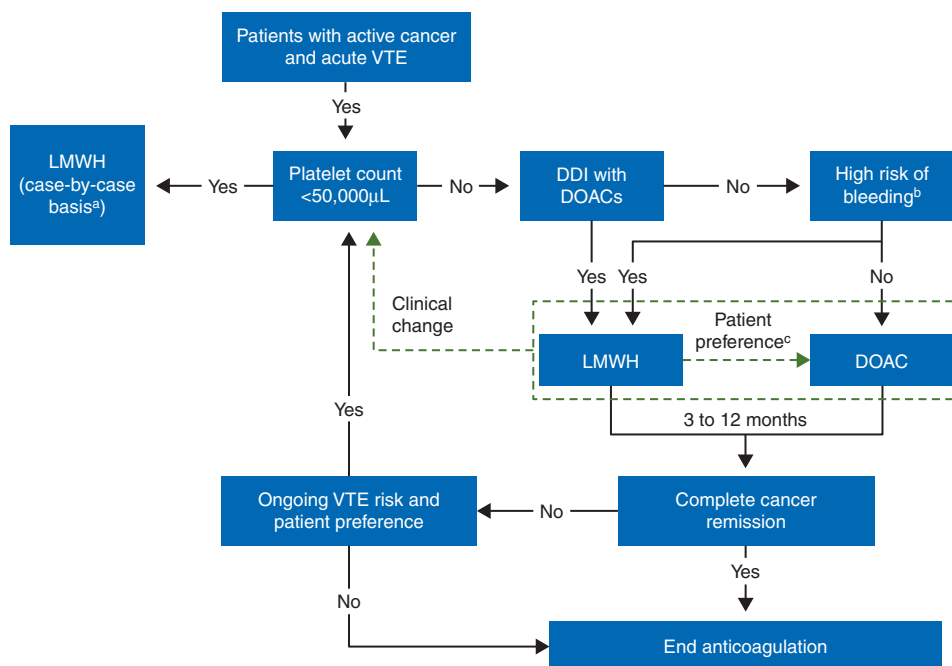
during edoxaban and rivaroxaban versus dalteparin treatment—in the ongoing apixaban trial. Such potential patient selection bias needs to be considered when CARAVAGGIO results become available, and careful evaluation of the patient populations will be necessary for any comparison among these trials of DOACs for treatment of cancer-associated VTE. Detailed analyses will be required to differentiate the safety profiles of apixaban, edoxaban, and rivaroxaban in patients with cancer.

An often-understated benefit of DOAC therapy relative to LMWH is the effect of longer treatment duration due to better patient persistence. In a recent large observational study including patients with cancer-associated VTE treated with LMWH or rivaroxaban, median duration of therapy was significantly shorter for LMWH versus rivaroxaban (1 versus 3 months) [36]. Although the rates of VTE recurrence were initially similar, they began to diverge in favor of rivaroxaban versus LMWH treatment after ~6 weeks; this divergence might reflect LMWH treatment discontinuation [36]. Even in the randomized clinical trial setting, Hokusai-VTE recorded numerically longer drug exposure, higher rate of study treatment completion, and lower rate of patients discontinuing treatment due to dosing inconvenience for edoxaban versus dalteparin [46]. These differences in treatment duration could contribute to the numerically lower VTE recurrence rate in patients receiving edoxaban versus dalteparin [46]. Better treatment persistence with DOACs versus LMWH is likely to be a strong consideration in anticoagulant selection for VTE treatment in patients with cancer.

Even with publication of new and ongoing studies, the evidence for DOAC treatment of cancer-associated VTE has limitations that should prompt further research. First, patient selection for clinical trials may not reflect the entire patient population;

results from observational studies should be helpful in this regard. Second, there remains little evidence on optimal duration of anticoagulation or choice of anticoagulant for VTE treatment longer than 6–12 months in patients with cancer [69, 70]. Finally, the new studies give an overview of DOAC treatment of patients with cancer-associated VTE but provide little guidance on which patients are most likely to benefit from DOAC therapy. Additional studies in patients with well-defined risk profiles are necessary to determine which patients are most likely to benefit from prevention of VTE recurrence or suffer from bleeding events during DOAC treatment.

Prevention of cancer-associated VTE is another potential use for DOACs. Thromboprophylaxis is recommended for hospitalized patients with active cancer and patients undergoing major cancer surgery, and suggested for outpatients with specific cancer types with a very high risk of VTE—such as advanced pancreatic cancer—with LMWH as the preferred agent [12, 17, 71]. Two recent randomized, double-blind, placebo-controlled studies provide data on DOAC use in ambulatory cancer patients. In the Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients (AVERT) study, objectively documented major VTE—defined as proximal DVT or pulmonary embolism—occurred in significantly fewer apixaban-treated patients [12/288 (4.2%)] versus placebo-treated patients [28/275 (10.2%);  $P < 0.001$ ] with a Khorana score  $\geq 2$  initiating a new course of chemotherapy for cancer treatment [72]. However, major bleeding occurred significantly more frequently in patients treated with apixaban versus placebo [10/288 (3.5%) versus 5/275 (1.8%);  $P = 0.046$ ] [72]. Similarly, ambulatory patients with a solid tumor or lymphoma and Khorana score  $\geq 2$  treated with rivaroxaban compared with placebo in the CASSINI trial had a



**Figure 1.** Potential treatment approach for cancer-associated VTE based on current treatment guidelines and new randomized controlled trial evidence. <sup>a</sup>Reduced dose or full dose following transfusion. <sup>b</sup>Includes patients with gastrointestinal cancer as well as risk factors unrelated to cancer. <sup>c</sup>On a case-by-case basis with an understanding of the relative risks and benefits. DDI, drug–drug interactions; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.



numerically lower rate of a composite of VTE events [25/420 (6.0%) versus 37/421 (8.8%);  $P=0.10$ ] and numerically higher rate of major bleeding [8/405 (2.0%) versus 4/404 (1.0%)] [73]. The AVERT and CASSINI trials showed that thromboprophylaxis with a DOAC was effective and associated with a low bleeding rate in ambulatory patients with cancer considered to have intermediate-to-high risk of VTE. However, the clinical benefit of DOACs for primary thromboprophylaxis still needs to be established.

Based on the evidence presented, DOACs appear to be reasonable and often preferable alternatives to LMWH for management of VTE in patients with cancer without potential drug–drug interactions with chemotherapy or high risk for bleeding, especially when patient preference or practical considerations threaten persistence with LMWH therapy. Figure 1 shows a potential treatment approach based on current treatment guidelines and the new randomized controlled clinical trial evidence summarized here. In patients with VTE and gastrointestinal cancer, DOAC use should be considered on a case-by-case basis and with an understanding of the RR and benefits. Ongoing research is still needed to provide additional insight into any potential class effects of factor Xa inhibitors in patients with cancer, on the relative efficacy of thromboprophylaxis with DOACs, and on management of drug–drug interactions between DOACs and anticancer agents.

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