NCCN Guidelines® Insights

Cancer-Associated Venous Thromboembolic Disease, Version 2.2018

Featured Updates to the NCCN Guidelines

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Abstract

Venous thromboembolism (VTE) is common in patients with cancer and increases morbidity and mortality. VTE prevention and treatment are more complex in patients with cancer. The NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease outline strategies for treatment and prevention of VTE in adult patients diagnosed with cancer or in whom cancer is clinically suspected. These NCCN Guidelines Insights explain recent changes in anticoagulants recommended for the treatment of cancer-associated VTE.

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Release date: November 10, 2018; Expiration date: November 10, 2019

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease

Disclosure of Relevant Financial Relationships

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THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

- Anticoagulation options recommended for management of VTE in patients with cancer include regimens involving only one agent (monotherapy options) as well as regimens that use more than one type of agent (combination therapy options). This section lists the recommended regimens, including dosing and duration, as well as a list of contraindications and warnings to help guide treatment selection.[1]
- **Select regimen based on: Renal failure (C_{cr} <30 mL/min), inpatient/outpatient, FDA approval, cost, ease of administration, monitoring, bleeding risk assessment, and ability to reverse anticoagulation. (See Contraindications and Warnings on VTE-E, 4 of 5).**
- Baseline laboratory testing: CBC, renal and hepatic function panel, aPTT, and PT/INR.
- **Follow institutional standard operating procedures (SOPs) for dosing schedules. If no SOPs then use the American College of Chest Physicians (ACCP) recommendations.[2]**
- **Following initiation of anticoagulant: Hemoglobin, hematocrit, and platelet count at least every 2–3 days for the first 14 days and every 2 weeks thereafter or as clinically indicated.**

Monotherapy Options

Agent(s)	Dosing Details[c]
LMWH – preferred for first 6 months in patients with proximal DVT or PE and for prevention of recurrent VTE in patients with advanced metastatic cancer.	
• Dalteparin (category 1)	**200 units/kg SC daily for 30 days, then 150 units/kg once daily for 2–6 months[a,3,4]**
• Enoxaparin	**1 mg/kg SC every 12 hours[d,5-8]**
Rivaroxaban	15 mg orally BID for 21 days, then 20 mg daily[9-12]
Fondaparinux	5 mg [<50 kg]; 7.5 mg [50–100 kg]; 10 mg [>100 kg] SC daily[13,14]
Unfractionated heparin (UFH) (category 2B)	
• UFH IV then SC	IV 80 units/kg load, then 18 units/kg/h, target aPTT of 2–2.5 x control or per hospital SOPs, then SC 250 units/kg every 12 hours[15]
• UFH SC	SC 333 unit/kg load, then SC 250 units/kg every 12 hours[15,16]
For patients who refuse or have compelling reasons to avoid LMWH,[b] the following direct oral anticoagulants (DOACs) are acceptable alternatives for management of VTE:	
• Apixaban	10 mg orally BID for 7 days, then 5 mg BID[17,18]

See next page for Combination Therapy Options

References available online in the full version of this guideline at NCCN.org [VTE-E 5 of 5]

[a]Although each of the LMWH agents has been studied in randomized controlled trials in cancer patients, the efficacy of dalteparin in this population is supported by the highest quality evidence and is the only LMWH approved by the FDA for this indication.[3,19]

[b]Patients may refuse or be poor candidates for LMWH injections because they are painful, inconvenient, and expensive. These factors may contribute to poor compliance with long-term LMWH treatment.

[c]For recommended duration, see Duration of Anticoagulation as Recommended by Guideline on VTE-E, 3 of 5.

[d]Long-term management with enoxaparin dosing of 1 mg/kg SC every 12 hours has not been tested in cancer patients.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in patients with cancer.[1,2] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Associated Venous Thromboembolic Disease outline strategies to prevent and treat VTE in adult patients (≥18 years) either with a diagnosis of cancer or in whom cancer is clinically suspected. In the guidelines, VTE is broadly defined to include deep venous thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT), and splanchnic vein thrombosis (SPVT).

Depending on the absence of contraindications and other patient- and case-specific factors, therapeutic anticoagulation is a key component of management of cancer-associated VTE. The specific contexts in which therapeutic anticoagulation is recommended for DVT, catheter-related DVT, PE, and acute SPVT are shown on DVT-2, DVT-3, PE-2,

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

Combination Therapy Options

Combinations with Warfarin

Agents	Dosing Details	
	Parenteral Dosing for 5–10 Days	Warfarin Dosing for at Least 6 Months[c]
LMWH + warfarin options:	LMWH dosing options:	• Warfarin (2.5–5 mg every day initially, subsequent dosing based on INR value; target INR 2–3)[20-22] ‣ If warfarin is selected for chronic anticoagulation, initiate warfarin concurrently with the parenteral agent used for acute therapy and continue both therapies for at least 5 days and until the INR ≥2 for 24 hours. ‣ During the transition to warfarin monotherapy, the INR should be measured at least twice weekly. Once the patient is on warfarin alone, the INR should be measured initially at least once weekly. Once the patient is on a stable dose of warfarin with an INR between 2 and 3, INR testing can be gradually decreased to a frequency no less than once monthly.
• Dalteparin + warfarin	• Dalteparin 200 units/kg SC daily[19]	
• Enoxaparin + warfarin	• Enoxaparin 1 mg/kg SC every 12 hours[5]	
Fondaparinux + warfarin	Fondaparinux dosing: 5 mg [<50 kg]; 7.5 mg [50–100 kg]; 10 mg [>100 kg] SC daily[13,14]	
UFH + warfarin options:	UFH dosing options:	
• UFH IV + warfarin	• UFH IV 80 units/kg load, then 18 units/kg/h, target aPTT of 2–2.5 x control or per hospital SOPs[15]	
• UFH SC + warfarin	• UFH SC 333 units/kg load, then 250 units/kg every 12 hours[15]	

Combinations with Edoxaban

Agents	Dosing Details	
	Parenteral Dosing for 5–10 Days[d]	Edoxaban Dosing
LMWH + edoxaban (category 1)	LMWH dosing options: • Dalteparin 200 units/kg SC daily[19] • Enoxaparin 1 mg/kg SC every 12 hours[5]	After completion of at least 5 days of parenteral anticoagulant, switch to edoxaban 60 mg daily (or 30 mg in patients with Cockcroft-Gault estimated creatinine clearance 30–50 mL/min or weight <60 kg or concomitant potent p-glycoprotein inhibitors or inducers), continuing for at least 6 months[c,23,24]
UFH + edoxaban	UFH dosing options: • UFH IV 80 units/kg load, then 18 units/kg/h, target aPTT of 2–2.5 x control or per hospital SOPs[15] • UFH SC 333 units/kg load, then 250 units/kg every 12 hours[15]	

References available online in the full version of this guideline at NCCN.org [VTE-E 5 of 5]

[c]For recommended duration, see Duration of Anticoagulation as Recommended by Guideline on VTE-E, 3 of 5.
[d]Unlike warfarin, concurrent administration with parenteral anticoagulants is not recommended when transitioning to edoxaban. See prescribing information for protocols for transitioning between agents.

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and SPVT-2 of the NCCN Guidelines for VTE (see full guidelines, available at NCCN.org). As shown on SVT-1 and SPVT-2, there are also some subsets of patients with SVT or chronic SPVT in which the NCCN Guidelines recommend anticoagulation or consideration of anticoagulation as a component of treatment (see full NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease, available at NCCN.org). Due to the emergence of new data on the efficacy and safety of anticoagulants in patients with cancer-associated VTE, NCCN recommendations for the treatment of cancer-associated VTE have changed dramatically in recent years. These NCCN Guidelines Insights review prospective randomized trial data supporting the current recommended options, including data supporting the use of direct oral anticoagulants (DOACs), and guidelines for patient selection and safe administration of these agents.

Use of Anticoagulants in Patients With VTE and Cancer: Clinical Data

Therapeutic anticoagulation regimens include combination therapy regimens in which one agent is used initially (as "acute" treatment) and then switched to a different agent that is used for long-term or chronic treatment (eg, ≥3 months), and monotherapy regimens in which the same agent is used for both acute and chronic treatment. Since the duration of "acute" treatment varies across regimens, the NCCN Guidelines list complete therapeutic anticoagulation regimens, including initial and long-term dosing, timing for changes in agents or dosing, and considerations for determining appropriate duration of treatment (VTE-E, pages 1291–1294).

Low Molecular Weight Heparin Alone Versus With Vitamin K Antagonist

For many years low molecular weight heparin (LMWH) alone or in combination with warfarin was the standard anticoagulation treatment for

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Combinations with Dabigatran

For patients who refuse or have compelling reasons to avoid long-term LMWH,[b] the following combination regimens are acceptable alternatives:

Agents	Dosing Details	
	Parenteral Dosing for 5–10 Days[e]	Dabigatran Dosing
LMWH + dabigatran	**LMWH dosing options:** • **Dalteparin 200 units/kg SC daily[19]** • **Enoxaparin 1 mg/kg SC every 12 hours[5]**	After completion of at least 5 days of parenteral anticoagulant, switch to dabigatran 150 mg orally BID (for patients with CrCl >30 mL/min only), continue for at least 6 months[c,e,25,26]
UFH + dabigatran	**UFH dosing options:** • **UFH IV 80 units/kg load, then 18 units/kg/h, target aPTT of 2–2.5 x control or per hospital SOPs[15]** • **UFH SC 333 units/kg load, then 250 units/kg every 12 hours[15]**	

Duration of Anticoagulation as Recommended by Guideline:

- **Minimum time of 3 months**
- **For non-catheter-associated DVT or PE recommend indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist.**
- **For catheter-associated thrombosis, anticoagulate as long as catheter is in place. Recommended total duration of therapy is at least 3 months.**
- **Providers should continue to discuss with patients the risks/benefits of anticoagulation to determine the appropriate duration of therapy. (See Elements for Consideration in Decision Not to Treat [VTE-G])**

References available online in the full version of this guideline at NCCN.org [VTE-E 5 of 5]

[b]Patients may refuse or be poor candidates for LMWH injections because they are painful, inconvenient, and expensive. These factors may contribute to poor compliance with long-term LMWH treatment.
[c]For recommended duration, see below.
[e]Unlike warfarin, concurrent administration with parenteral anticoagulants is not recommended when transitioning to dabigatran. See prescribing information for protocols for transitioning between agents.

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cancer-associated VTE. Several prospective randomized studies have compared the efficacy and safety of single-agent LMWH (for initial and long-term treatment) versus combination therapy with initial LMWH or unfractionated heparin (UFH) plus long-term treatment with vitamin K antagonist (VKA) (Tables 1 and 2).[3–7]

In the 4 trials that reported VTE recurrence data,[4–7] rates with single-agent LMWH were lower than those for LMWH plus VKA, although these trends reached statistical significance in only 2 of the 4 trials (Table 1). Although there was no difference in recurrent VTE between treatment arms during the 12-week study period in the Main-LITE study, recurrent VTE was significantly lower at 12 months with single-agent LMWH (tinzaparin) compared with UFH plus warfarin (7% vs 16%; P=.044; relative risk, 0.44).[6]

Trends in rates of major bleeding were not consistent across trials (Table 1). CANTHANOX found that major bleeding was significantly less frequent with single-agent enoxaparin compared with enoxaparin plus warfarin.[3] In contrast, major bleeding did not differ by treatment arm in the other 4 studies (Table 1). CANTHANOX also showed that single-agent enoxaparin was associated with less fatal bleeding compared with enoxaparin plus warfarin (0% vs 8% of patients; P=.03).[3] Two studies (CLOT, ONCENOX) reported nonsignificant trends toward more major bleeding with single-agent LMWH.[4,5]

Taken together, results from these randomized trials show that in patients with cancer-associated VTE, LMWH is associated with a similar or lower risk of VTE and similar risk of major bleeding compared with LMWH/UFH plus VKA. In addition, no difference was seen in overall survival between LMWH and UFH/LMWH plus VKA, although the vast majority of study death was due to progressive cancer.[3–7] There were no consistent trends regarding VTE- or bleeding-associated fatalities between treatment arms. Meta-analyses of randomized controlled trials have consistently shown that LMWH is supe-

ANTICOAGULANT OPTIONS: CONTRAINDICATIONS AND WARNINGS

Agent(s)	Contradictions and Warnings
LMWH	• Use with caution in patients with renal dysfunction. Consider dose adjustments or alternative therapy for patients with severe renal disfunction (CrCl <30 mL/min). • Follow package insert for renal dysfunction and body weight dosing. • Anti-Xa monitoring (peak and trough) of LMWH has been recommended for patients with severe renal dysfunction, although limited data are available to support the clinical relevance of anti-Xa levels. • Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Fondaparinux	• Contraindicated in patients with CrCl <30 ml/min • Use with caution in patients with moderate renal insufficiency (CrCl 30–50 mL/min), weight <50 kg, or age >75 y
UFH	• Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Warfarin	Relative contraindications: • Concomitant inhibitors and inducers of CYP2C9, 1A2, or 3A4
Apixaban, dabigatran, edoxaban, and rivaroxaban	Contraindications: • Stage IV chronic kidney disease: ‣ Apixaban[f]: CrCl <25 mL/min ‣ Dabigatran, edoxaban, and rivaroxaban: CrCl <30 mL/min • Active/clinically significant liver disease: ‣ Apixaban or edoxaban: ALT/AST >2 x ULN; total bilirubin >1.5 x ULN ‣ Dabigatran or rivaroxaban: ALT/AST >3x ULN • Strong dual inhibitors/inducers of CYP3A4 and P-glycoprotein (P-gp): see prescribing information for rivaroxaban[9] and apixaban[17] • Inducers/inhibitors of P-gp: see prescribing information for dabigatran[25] and edoxaban[23] Relative contraindications, use with caution: • DOACs have been associated with urinary and intestinal tract bleeding, and should be used with caution in patients with urinary or gastrointestinal tract lesions, pathology, or instrumentation. • Use with caution in patients with compromised renal or liver function. • For patients receiving nephrotoxic or hepatotoxic chemotherapy consider monitoring patients more closely with laboratory testing. • Consider drug-drug interactions.

References available online in the full version of this guideline at NCCN.org [VTE-E 5 of 5]

[f]Although stage IV chronic kidney disease is not listed as a contraindication in the FDA-approved label for apixaban, the NCCN Panel avers that there are insufficient data to support safe apixaban dosing in these patients, especially those who are on hemodialysis.

rior to VKA for the prevention of recurrent VTE, with no difference in major bleeding in the chronic treatment of VTE in patients with cancer.[8–11] No difference in survival was noted between anticoagulation regimens.[9,11] Based on these results and more than a decade of real-world experience, the NCCN Guidelines list single-agent LMWH as a preferred anticoagulation option for cancer-associated VTE (see VTE-E 1 of 5, page 1291). Results of the CLOT study support use of single-agent dalteparin as a category 1 preferred option for anticoagulation of cancer-associated acute VTE, as this study showed a significant reduction in recurrent VTE with no increase in major bleeds.[4] This category 1 recommendation applies specifically to the dalteparin regimen used in the trial (Table 2) for a duration of 6 months.

Because trials including patients with cancer have not compared LMWH with VKAs for a duration of >6 months, decisions regarding continued LMWH therapy beyond this time frame or transition to a VKA should be based on clinical judgment.

Combinations With Warfarin

Combining LMWH or UFH With Warfarin: Given that patients have great difficulty with long-term adherence to parenteral agents and the higher cost of LMWH, the NCCN Guidelines also include combinations of LMWH/UFH plus warfarin among the recommended options for treatment of cancer-associated VTE (see VTE-E 2 of 5, page 1292). The recommended LMWH dosing in these combination regimens reflects the regimens used in the comparator arms of the CLOT trial (for dalteparin) and ONCENOX trial (for enoxaparin) (Table 2).

Combining Fondaparinux With Warfarin: Fondaparinux is a specific indirect factor Xa inhibitor FDA-approved for the treatment of acute DVT or PE when administered in conjunction with warfarin.[12] The prospective randomized MATISSE trials compared fondaparinux plus warfarin versus LMWH plus warfarin, or versus UFH plus warfarin, for treatment of DVT or PE, respectively[13,14] (Tables 3 and 4). In patients

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Table 1. LMWH Versus Warfarin for Long-Term Treatment of VTE in Patients With Active Cancer[a]: Data From Prospective Randomized Trials

Study (ClinicalTrials.gov Identifier)	VTE Index Event[b]	Initial Prestudy Tx Allowed[c]	Study Tx (Patients With Cancer)[d]	Study Tx Period[e]	Event Rate on Study (Events on Study/Patients at Risk, n)			
					Recurrent VTE		Major Bleeding	
CANTHANOX[3]	DVT or PE	LMWH/UFH ≤5 d	Enoxaparin (n=71)	3 mo	NR[f]		7.0% (5/71)	*P*=.09
			Enoxaparin + warfarin (n=75)				16.0% (12/75)	
CLOT[4]	Newly diagnosed acute symptomatic proximal DVT and/or PE	Heparin ≤48 h	Dalteparin (n=338)	6 mo	9%[g] (27/336)	*P*=.002 HR, 0.48; 95% CI, 0.30–0.77	6% (19/338)	*P*=.27
			Dalteparin + warfarin/ acenocoumarol (n=338)		17%[g] (53/336)		4% (12/335)	
ONCENOX[5]	Acute symptomatic VTE (DVT or PE)	LMWH/UFH ≤72 h	Enoxaparin (n=68)	180 d (6 mo)	6.6% (4/61)	NS	9.0% (6/67)	NS
			Enoxaparin + warfarin (n=34)		10.0% (3/30)		2.9% (1/34)	
Main-LITE Cancer[6]	Acute symptomatic proximal DVT[h] ± PE	UFH/LMWH/oral anticoagulant ≤2 d	Tinzaparin[i] (n=100)	12 wk (3 mo)	6% (6/100)	NS[j]	7% (7/100)	NS
			UFH + warfarin (n=100)		10% (10/100)		7% (7/100)	
CATCH (NCT01130025)[7]	Acute symptomatic proximal DVT[h] and/or PE	≤72 h	Tinzaparin[i] (n=449)	180 d (6 mo)	7.2%[k] (31/449)	*P*=.07 HR, 0.65; 95% CI, 0.41–1.03	2.7% (12/449)	*P*=.77 HR, 0.89; 95% CI, 0.40–1.99
			Tinzaparin[i] + warfarin (n=451)		10.5%[k] (45/451)		2.4% (11/451)	

Abbreviations: BCC, basal cell carcinoma; DVT, deep vein thrombosis; HR, hazard ratio; LMWH, low molecular weight heparin; NR, not reported; NS, statistical significance was not reached, but no *P* value, hazard ratio, or RR was reported; PE, pulmonary embolism; RR, risk ratio; Tx, treatment; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a]Active cancer definitions by trial:
CANTHANOX: solid tumor ± distant localization, or hematologic malignancy; active or in remission but with ongoing cancer treatment.
CLOT: cancer diagnosis or cancer treatment within 6 months of enrollment, or recurrent/metastatic cancer; excluding cutaneous BCC.
ONCENOX: active, residual malignancy with measurable disease, persistently elevated tumor markers, metastatic disease after debulking, or histologically/cytologically confirmed; excluding acute leukemia or localized skin cancer.
Main-LITE Cancer: no definition provided.
CATCH: histologic/cytologic confirmation and any of the following: diagnosis or anticancer treatment within 6 months; recurrent, regionally advanced, or metastatic, or not in complete remission from hematologic malignancy; excludes cutaneous BCC.

[b]Inclusion criteria for index VTE event. For all studies, the index VTE was required to be objectively documented/diagnosed. Most studies excluded catheter-associated VTE.

[c]Initial anticoagulant treatment (agent and duration) allowed before randomization.

[d]Anticoagulation treatment assigned by randomization. See Table 2 for details.

[e]Planned treatment duration.

[f]Composite end point of major bleeding or recurrent VTE was less frequent with long-term enoxaparin vs warfarin (10.5% vs 21.1% of patients; *P*=.09; RR, 2.02; 95% CI, 0.88–4.65)

[g]Kaplan-Meier estimate of 6-month rate (%) and crude incidence (n/N) of VTE recurrence.

[h]Proximal DVT was defined as DVT in the popliteal, femoral, or iliac veins.

[i]Tinzaparin is no longer available in the United States, but these data illustrate the efficacy and safety of LMWH for treatment of cancer-associated VTE.

[j]Recurrent VTE at 12 months showed significant improvement with tinzaparin vs UFH + warfarin (7% vs 16%; *P*=.044; RR, 0.44; 95% CI, 0.19–1.02).

[k]Cumulative incidence at 6 mo (%) and crude incidence (n/N).

with cancer in the MATISSE DVT and PE trials, no significant differences were noted in the rates of recurrent VTE or major bleeding between treatment arms; no significant differences in survival were observed. The NCCN Guidelines include combination therapy with fondaparinux and warfarin as an option for treatment of VTE in patients with cancer (see VTE-E 2 of 5, page 1292), with the recommended dose matching that used in the MATISSE trials.

Direct Oral Anticoagulants

Although the FDA approvals of the DOACs apixaban, dabigatran, edoxaban, and rivaroxaban for treatment of VTE were based on trials in which most patients did not have cancer,[15–20] subanalyses of patients with cancer have now been published for the pivotal trials testing each of these agents,[21–24] and results have now been reported from 2 randomized trials testing DOACs specifically in patients with cancer.[25,26] Table 5 summarizes the VTE index event criteria, overall treatment scheme, and key results from patients with cancer in each of these prospective randomized trials. Table 6 provides details about the anticoagulation regimens used in these trials. The following sections describe the data and rationale supporting each of the DOAC-containing regimens included in the guidelines among the recommended options for anticoagulation treatment of cancer-associated VTE.

Apixaban: Apixaban is an orally administered direct factor Xa inhibitor that has been FDA-approved for the treatment of DVT and PE based on results from the AMPLIFY trial, which compared single-agent apixaban with combination enoxaparin plus warfarin in patients with acute symptomatic proximal DVT and/or acute symptomatic PE (supplemental eTable 1, available with this article at JNCCN.org).[17,27] As shown in Table 5, the subanalysis of patients with

Table 2. LMWH Versus Warfarin for Long-Term Treatment of VTE in Patients With Active Cancer: Study Treatment Dosing

Study (ClinicalTrials.gov Identifier)	Study Arm	Study Treatment Dosing
CANTHANOX[3]	Enoxaparin	Enoxaparin: 1.5 mg/kg SC qd
	Enoxaparin + warfarin	Enoxaparin: 1.5 mg/kg SC qd for ≥4 d and until INR ≥2.0 on 2 consecutive days Warfarin: 6–10 mg initially, then dose-adjusted to INR 2.0–3.0
CLOT[4]	Dalteparin	Dalteparin: 200 IU/kg qd SC for 1 month, then ~150 IU/kg qd[a]
	Dalteparin + warfarin/acenocoumarol	Dalteparin: 200 IU/kg qd SC for 5–7 d and until INR >2.0 for 2 consecutive days Warfarin/Acenocoumarol: started ≤24 h after randomization, dose-adjusted to INR 2.5
ONCENOX[5]	Enoxaparin	Enoxaparin: 1.0 mg/kg SC bid for 5 days, then 1.0 mg/kg qd; or 1.0 mg/kg bid for 5 days, then 1.5 mg/kg qd
	Enoxaparin + warfarin	Enoxaparin: 1.0 mg/kg SC bid x ≥5 d and until stable INR 2.0–3.0 Warfarin: started day 2 after start of enoxaparin, dose-adjusted to INR 2.0–3.0
Main-LITE Cancer[6]	Tinzaparin	Tinzaparin: 175 IU/kg SC qd
	UFH + warfarin	UFH: 5,000 U or 80 U/kg bolus IV, then continuous IV, dose-adjusted by aPTT, ≥6 d until therapeutic INR reached Warfarin: 5–10 mg started day 1, then adjusted to INR 2.0–3.0
CATCH (NCT01130025)[7]	Tinzaparin	Tinzaparin: 175 IU/kg SC qd
	Tinzaparin + warfarin	Tinzaparin: 175 IU/kg qd x 5–10 d and until INR >2.0 for 2 consecutive days Warfarin: started concurrent with tinzaparin, dose-adjusted to INR 2.0–3.0

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; IV, intravenous; LMWH, low molecular weight heparin; SC, subcutaneous injection; UFH, unfractionated heparin.
[a]Dalteparin long-term dosing is approximately 150 IU/kg because patients used prefilled syringes according to their weight: 7,500 IU for ≤56 kg, 10,000 IU for 57–68 kg, 12,500 IU for 69–82 kg, 15,000 IU for 83–98 kg, and 18,000 IU for ≥99 kg.

active cancer at baseline showed no significant treatment-dependent differences in VTE recurrence or major bleeding, although there were nonsignificant trends toward better outcomes with apixaban.[21] Mortality at 3 months was similar across treatment arms. It is important to note that the study protocol allowed individual investigators the option of excluding patients with cancer whom they believed should be treated with LMWH. Consequently, the patients with cancer enrolled in the study were much healthier and had much lower mortality than those enrolled in the CLOT trial (6% and 7.7% at 3 months for apixaban and enoxaparin/warfarin in the AMPLIFY trial vs 39% and 41% at 6 months for dalteparin and oral anticoagulant in the CLOT trial, respectively).[4,21] Based on these results, the NCCN Guidelines include single-agent apixaban as an option for anticoagulation in patients with cancer-associated VTE (see VTE-E 1 of 5, page 1291). Because of the small number of patients with cancer (n=169), use of LMWH plus warfarin rather than LMWH alone (as the comparator), and the selection of healthier patients with cancer in the AMPLIFY study, this recommendation is limited to patients who refuse or have compelling reasons to avoid LMWH. Randomized studies comparing apixaban with LMWH in patients with active cancer are currently underway and should provide more conclusive evidence of apixaban's efficacy and safety in patients with cancer–associated VTE.

Dabigatran: Dabigatran is an orally administered direct thrombin inhibitor FDA-approved for the treatment of DVT and PE in patients who have received parenteral anticoagulant for 5 to 10 days.[28] This approved indication is based on results of the RE-COVER and RE-COVER II trials (supplemental eTable 1).[20] As shown in Table 5, analysis of the subset of patients with cancer at baseline showed no treatment-dependent differences in the rates of VTE recurrence or major bleeding.[22] Among patients with cancer, the mortality rates were not significantly different between treatment arms. Similar to the apixaban trials, the cancer subgroup in the dabigatran studies was substantially healthier than the CLOT trial population, as evidenced by the lower mortality (14% vs 39%).[4,22] Based on results from this subgroup analysis, the NCCN Guidelines include LMWH/UFH plus dabigatran as potential treatment options for cancer-associated VTE (see VTE-E 3 of 5, page 1293). Because of the limitations of the RE-COVER trials (comparison with LMWH plus warfarin, healthier population of patients with cancer), the recommendation for LMWH/UFH plus dabigatran is limited to those who refuse or have compelling reasons to avoid long-term LMWH.

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Table 3. Fondaparinux for VTE in Patients With Active Cancer[a]: Data From Prospective Randomized Trials

Study	VTE Index Event[b]	Initial Prestudy Tx Allowed[c]	Study Tx (Patients With Cancer)[d]	Study Tx Period[e]	Event Rate on Study (Events on Study/Patients at Risk, n)			
					Recurrent VTE		Major Bleeding	
MATISSE DVT subgroup with cancer[76]	Acute symptomatic DVT[f] without symptomatic PE	LMWH/oral anticoagulant ≤24 h[14]	Fondaparinux + VKA (n=126)	3 mo	12.7% (16/126)	*P*=.06 HR, 2.50; 95% CI, 0.98–6.38	7.1% (9/126)	*P*=.99
			Enoxaparin + VKA (n=111)		5.4% (6/111)		7.2% (8/111)	
MATISSE PE subgroup with cancer[76]	Acute symptomatic PE ± DVT	LMWH/oral anticoagulant ≤24 h[13]	Fondaparinux + VKA (n=112)	3 mo	8.9% (10/112)	*P*=.07 HR, 0.50; 95% CI, 0.24–1.07	3.6% (4/112)	*P*=.33
			UFH + VKA (n=128)		17.2% (22/128)		6.3% (8/128)	

Abbreviations: DVT, deep vein thrombosis; HR, hazard ratio; LMWH, low molecular weight heparin; PE, pulmonary embolism; Tx, treatment; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Active cancer definitions for MATISSE trials: cancer present at study entry or treated within 6 mo prior
[b]Inclusion criteria for index VTE event. For all studies the index VTE was required to be objectively documented/diagnosed. Most studies excluded catheter-associated VTE.
[c]Initial anticoagulant treatment (agent and duration) allowed before randomization.
[d]Anticoagulation treatment assigned by randomization. See Table 4 for details.
[e]Planned duration of study treatment
[f]Acute symptomatic DVT permitted only if of the popliteal, femoral, iliac, or trifurcation of calf veins.

Edoxaban: Edoxaban is an orally administered direct factor Xa inhibitor that is FDA approved for the treatment of DVT or PE after 5 to 10 days of initial therapy with a parenteral anticoagulant.[29] The FDA-approved indication is based on results from the Hokusai-VTE study, a prospective randomized trial that tested edoxaban in patients with acute lower extremity DVT and/or acute PE (supplemental eTable 1).[18] Results from subgroup analyses showed that although there were no treatment-dependent differences in recurrent VTE rates among patients with no history of cancer and no active cancer while on study (3% vs 3% for edoxaban vs warfarin), there was a trend toward higher rates of recurrent VTE with warfarin in the subset of patients with active cancer at baseline (Table 5), which reached significance for the subgroup that included all patients with current or prior cancer at baseline (4% [14/378] vs 7% [28/293]; hazard ratio, 0.53; 95% CI, 0.28–1.00; *P*=.0007).[23] Rates of major bleeding did not differ across treatment arms in any of the subgroups based on current/prior cancer status.[18,23] Mortality was similar across treatment arms for all categories of patients with current or prior cancer.

Given that single-agent LMWH is the preferred option for the treatment of VTE in patients with cancer, a separate randomized trial specifically in patients with cancer (Hokusai VTE-Cancer) compared LMWH plus edoxaban combination therapy (initial short-term LMWH followed by longer-term edoxaban) with single-agent LMWH (dalteparin) for the treatment of acute lower extremity DVT or acute PE.[25] As shown in Table 5, the rate of recurrent VTE was lower in those who received combination LMWH plus edoxaban versus single-agent dalteparin, although this trend did not reach significance and the rate of major bleeding was significantly higher in the edoxaban arm. Mortality was not significantly different between treatment arms, and the vast majority of deaths were cancer related. The numbers of VTE- or bleed-related deaths were too small to allow for meaningful comparisons across treatment arms. Based on these results, the NCCN Guidelines include combination treatment with LMWH followed by edoxaban as a category 1 option for anticoagulation of cancer-associated VTE and combination therapy with initial UFH followed by edoxaban as a category 2A option because it was not

Table 4. Fondaparinux for VTE in Patients With Active Cancer: Study Treatment Dosing[a]

Study	Regimen	Study Treatment Dosing
MATISSE DVT[14,76]	Fondaparinux + VKA	Fondaparinux: 5.0, 7.5, 10.0 mg for <50 kg, 50–100 kg, >100 kg, respectively; SC qd for ≥5 d and until INR >2.0 for 2 consecutive days Enoxaparin: 1 mg/kg SC bid for ≥5 days and until INR >2.0 for 2 consecutive days VKA: started within 72 hours of start of initial therapy, dose-adjusted to INR 2.0–3.0
	Enoxaparin + VKA	
MATISSE PE[13,76]	Fondaparinux + VKA	Fondaparinux: 5.0, 7.5, 10.0 mg for <50 kg, 50–100 kg, >100 kg, respectively; SC qd for ≥5 days and until INR >2.0 for 2 consecutive days UFH: initial bolus ≥5,000 IU, then ≥1,250 IU/h IV adjusted to maintain aPTT 1.5–2.5 x control for ≥5 days and until INR >2.0 for 2 consecutive days VKA: started within 72 hours of start of initial therapy, dose-adjusted to INR 2.0–3.0
	UFH + VKA	

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; IV, intravenous; SC, subcutaneous injection; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Active cancer definitions for MATISSE trials: cancer present at study entry or treated within 6 mo prior.

Table 5. DOACs for Treatment of VTE in Patients With Active Cancer[a]: Data From Prospective Randomized Trials

Study (ClinicalTrials.gov Identifier)	VTE Index Event[b]	Initial Prestudy Tx Allowed[c]	Study Tx (Patients With Cancer)[d]	Study Tx Period[e]	Event Rate (Events/Patients at Risk, n)			
					Recurrent VTE		Major Bleeding	
Subgroup analyses of patients with cancer								
AMPLIFY[21]	Acute symptomatic proximal DVT[f] and/or acute symptomatic PE	≤2 doses of qd LMWH/ fondaparinux/ VKA, ≤3 doses of bid LMWH, ≤36 h UFH IV[17]	Apixaban (n=88)	6 mo	3.7% (3/81)	RR, 0.56; 95% CI, 0.13–2.37	2.3% (2/87)	RR, 0.45; 95% CI, 0.08–2.46
			Enoxaparin + warfarin (n=81)		6.4% (5/78)		5.0% (4/80)	
RE-COVER (NCT00291330) + RE-COVER II (NCT00680186)[22]	Acute symptomatic proximal DVT of legs or PE	N/A[g]	Parenteral + dabigatran (n=114)	6 mo	3.5% (4/114)	HR, 0.74; 95% CI, 0.20–2.7	3.8% (4/105)	HR, 1.23; 95% CI, 0.28–5.5
			Parenteral + warfarin (n=107)		4.7% (5/107)		3.0% (3/100)	
Hokusai-VTE (NCT00986154)[23]	Acute lower extremity DVT[h] and/or acute PE[h]	≤48 h LMWH/UFH/ fondaparinux, ≤1 dose VKA[18]	LMWH/UFH + edoxaban (n=85)	3–12 mo (12 mo)	2% (2/85)	HR, 0.30; 95% CI, 0.06–1.51	5% (4/85)	HR, 1.67; 95% CI, 0.34–8.11
			LMWH/UFH + warfarin (n=77)		9% (7/77)		3% (2/77)	
EINSTEIN-DVT (NCT00440193) + EINSTEIN-PE (NCT00439777)[24]	EINSTEIN-DVT: acute symptomatic DVT without PE EINSTEIN-PE: acute symptomatic PE ± DVT	UFH/LMWH/ fondaparinux ≤48 h; VKA ≤1 dose	Rivaroxaban (n=354)	3, 6, or 12 mo	5% (16/354)	*P*=.24	2% (8/353)	*P*=.047
			Enoxaparin + VKA (n=301)		7% (20/301)	HR, 0.67; 95% CI, 0.35–1.30	5% (15/298)	HR, 0.42; 95% CI, 0.18–0.99
Trials including only patients with cancer								
Hokusai VTE-Cancer (NCT02073682)[25]	Acute lower-extremity DVT[h] or acute PE[h]	≤72 h of therapeutic LMWH, UFH, fondaparinux, DOAC or VKA	LMWH + edoxaban (n=525)	6–12 mo (12 mo)	7.9% (41/522)	*P*=.09	6.9% (36/522)	*P*=.04
			Dalteparin (n=525)		11.3% (59/524)	HR, 0.71; 95% CI, 0.48–1.06	4.0% (21/524)	HR, 1.77; 95% CI, 1.03–3.04
SELECT-D[26]	Symptomatic/ Incidental PE or symptomatic lower-extremity DVT	≤96 h anticoagulant or aspirin >75 mg/d	Rivaroxaban (n=203)	6 mo	4%[i] (8/203)	HR, 0.43; 95% CI, 0.19–0.99	6%[i] (11/203)	HR, 1.83; 95% CI, 0.68–4.96
			Dalteparin (n=203)		11%[i] (18/203)		4%[i] (6/203)	

Abbreviations: BCC, basal cell carcinoma; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HR, hazard ratio; IV, intravenous; LMWH, low molecular weight heparin; N/A, not applicable; PE, pulmonary embolism; RR, risk ratio; SCC, squamous cell carcinoma; Tx, treatment; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Active cancer definitions by trial:
EINSTEIN studies: active cancer at baseline or emerging during study (active cancer at baseline: cancer diagnosis or treatment within 6 months before enrolment, or recurrent/metastatic cancer; active cancer emerging during study: new diagnosis or recurrence after randomization).
AMPLIFY: cancer diagnosed or treated within the past 6 months.
Hokusai-VTE: per post hoc assessment, defined as presence of solid measurable cancer or hematologic malignancy not in remission; not nonmelanoma skin cancer. Another 175 patients developed cancer during the study.
Hokusai VTE-Cancer: diagnosed within the previous 2 years, or treated within the past 6 months, or regionally advanced/metastatic, or hematologic not in complete remission; not cutaneous BCC or SCC.
RE-COVER and RE-COVER II: diagnosis of cancer or any treatment of cancer ≤5 y before enrollment, or recurrent or metastatic cancer; not cutaneous BCC or SCC.
SELECT-D: cancer diagnosed or treated within the prior 6 months, or recurrent/metastatic, or hematologic not in complete remission; not cutaneous BCC or SCC.
[b]Index VTE was objectively documented/diagnosed. Most studies excluded catheter-associated VTE.
[c]Initial anticoagulant treatment (agent and duration) allowed prior to randomization.
[d]Anticoagulation treatment assigned by randomization. See Table 6 for details. Number of patients with active cancer.
[e]Planned duration of study treatment. Study period used for analysis of the recurrent VTE and major bleed rates is shown in parentheses if different from planned treatment duration.
[f]In AMPLIFY, qualifying DVT index event must be at least popliteal or more proximal vein.
[g]In the RE-COVER trials initial parenteral anticoagulant was required but could start before randomization.
[h]In Hokusai-VTE and Hokusai VTE-Cancer, qualifying DVT and PE events could be symptomatic or unsuspected. Lower-extremity DVT included DVT of the popliteal, femoral, or iliac vein or inferior vena cava. For Hokusai VTE-Cancer, qualifying incidental PE must involve the segmental or more proximal pulmonary arteries.
[i]Cumulative incidence at 6 months (%) and crude incidence (n/N).

tested in the Hokusai VTE-Cancer trial (see VTE-E 2 of 5, page 1292). The recommended edoxaban dosing matches that used in the Hokusai trials (see Table 2) and the prescribing information.[29]

Rivaroxaban: Rivaroxaban is an orally administered direct factor Xa inhibitor approved by the FDA as a single-agent treatment for DVT and/or PE.[30] FDA approval for this indication was based on the results of 2 phase 3 open-label noninferiority randomized trials comparing single-agent rivaroxaban versus initial short-term LMWH (enoxaparin) plus warfarin/ acenocoumarol (started concurrently with LMWH and continued as single agent after LMWH discontinuation; See Table 6 for details on regimens tested, supplemental eTable 1 for results).[15,16,31] As shown in Table 5, pooled analysis of the subset of patients with active cancer (at baseline or presenting during the study) in these trials yielded similar results as the larger pooled analysis, with no treatment-dependent

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Table 6. DOACs for Treatment of VTE in Patients With Active Cancer: Study Treatment Dosing

Study (ClinicalTrials.gov identifier)	Regimen	Study Treatment Dosing
Subgroup analyses of patients with cancer		
AMPLIFY[17,21]	Apixaban	Apixaban: 10 mg bid for 7 d, then 5 mg bid
	Enoxaparin + warfarin	Enoxaparin: 1 mg/kg bid for ≥5 d and until INR ≥2.0 Warfarin: started concurrently with enoxaparin, dose-adjusted to INR 2.0–3.0
RE-COVER (NCT00291330) + RE-COVER II (NCT00680186)[20,22]	Parenteral + dabigatran Parenteral + warfarin	Parenteral: UFH, LMWH or fondaparinux for ≥5 d until INR ≥2.0 for 2 consecutive days Dabigatran: 150 mg bid started after parenteral stopped Warfarin: started with parenteral, dose adjusted to INR 2.0–3.0
Hokusai-VTE (NCT00986154)[18,23]	LMWH/UFH + edoxaban LMWH/UFH + warfarin	LMWH: enoxaparin 1 mg/kg bid or 1.5 mg/kg qd for ≥5 days and until INR ≥2.0 for 2 consecutive days UFH: 5,000 IU bolus + 1,300 IU/h IV, adjusted to aPTT, for ≥5 d and until INR ≥2.0 for 2 consecutive days Edoxaban: started after LMWH/UFH stopped, 60 mg qd[a] Warfarin: started concurrently with LMWH/UFH, dose-adjusted to INR 2.0–3.0
EINSTEIN-DVT (NCT00440193) + EINSTEIN-PE (NCT00439777)[24]	Rivaroxaban	Rivaroxaban: 15 mg bid for 21 days, then 20 mg qd
	Enoxaparin + VKA	Enoxaparin: 1 mg/kg SC bid for ≥5 d and until INR ≥2.0 for 2 consecutive days VKA: started within 48 h of randomization, dose-adjusted to INR 2.0–3.0
Trials including only patients with cancer		
Hokusai VTE-Cancer (NCT02073682)[25]	LMWH + edoxaban	LMWH: therapeutic doses for ≥5 d Edoxaban: 60 mg d[a]; started after LMWH stopped
	Dalteparin	Dalteparin: 200 IU/kg SC qd for 1 mo, then 150 IU/kg SC qd
SELECT-D[26]	Rivaroxaban	Rivaroxaban: 15 mg bid for 3 wk, then 20 mg qd
	Dalteparin	Dalteparin: 200 IU/kg SC qd for 1 mo, then 150 IU/kg SC qd

Abbreviations: aPTT, activated partial thromboplastin time; DOAC, direct oral anticoagulant; INR, international normalized ratio; IV, intravenous; LMWH, low molecular weight heparin; SC, subcutaneous injection; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Adjusted edoxaban dosing: 30 mg qd for creatinine clearance of 30–50 mL/min or body weight ≤60 kg or concomitant P-glycoprotein inhibitors.

difference in the rate of recurrent VTE and a small but significant decrease in major bleeding with rivaroxaban.[24] Mortality rates were not significantly different across treatment arms, both for patients with cancer and without cancer.

Given that single-agent LMWH is the preferred option for patients with cancer, the randomized open-label pilot Select-D trial compared single-agent rivaroxaban with single-agent LMWH (dalteparin) for the treatment of PE or symptomatic lower extremity DVT in patients with cancer.[26] As shown in Table 5, the cumulative rate of VTE recurrence at 6 months was lower with rivaroxaban, but the cumulative major bleed rate was slightly higher with rivaroxaban.[26] Overall survival at 6 months did not differ by treatment, and the numbers of deaths related to VTE or bleeds were too small to allow for meaningful comparison.

Based on these results, the NCCN Guidelines include single-agent rivaroxaban as an option for anticoagulation treatment of VTE in patients with cancer. Unlike single-agent apixaban, the recommendation for single-agent rivaroxaban is not limited to patients with compelling reasons to avoid LMWH, because the Select-D trial showed that rivaroxaban has similar or better efficacy than single-agent dalteparin in patients with cancer-associated VTE.[26] The recommended dosing regimen for rivaroxaban matches that used in the EINSTEIN and Select-D trials (Table 6) and recommended in the FDA label.[30]

Selection Among Therapeutic Anticoagulation Options

Use of single-agent LMWH for treatment of cancer-associated VTE is challenging because LMWH is expensive and the injections are painful to administer; both factors negatively impact patient quality of life. Many studies of clinical practice patterns have shown that single-agent LMWH is underutilized in patients with cancer-associated VTE despite guideline recommendations that it is the preferred treatment option.[32–46] Compared with oral anticoagulants, LMWH is associated with poorer persistence, shorter duration of treatment, and a higher likelihood of switching to a different anticoagulant.[34,37,39,42,44,47–49] One prospective cohort study of patients with cancer-associated VTE found that 21% discontinued LMWH due to side effects, the most common being injection site pain, large local injection site hematomas, and allergic reactions.[47] In the Hokusai VTE-Cancer trial, nearly 15% of patients in the dalteparin arm decided to discontinue study treatment due to inconvenience of dosing, whereas only 4% in the edoxaban arm discontinued for this reason.[25]

Although physicians may be reluctant to prescribe long-term LMWH based on the assumption that outpatients are much more likely to adhere to a prescribed oral dosing than to daily painful subcutaneous injections, it is unclear to what degree poor patient adherence is a barrier to sufficient anticoagulation for cancer-associated VTE. In prospective trials, adherence to long-term LMWH regimens was remarkably high among patients with cancer-associated VTE (supplemental eTable 2). In the 2 prospective randomized trials that compared single-agent LMWH to a DOAC-containing regimen for treatment of VTE in cancer patients (Hokusai VTE-Cancer and Select-D), results showed no significant difference between treatment arms in the level of adherence to the study protocol (supplemental eTable 2). One prospective observational study in patients prescribed long-term LMWH for cancer-associated VTE found that although the overall adherence to guidelines was only 55%, the mean duration of LMWH treatment was consistent with guidelines.[50] This and other studies that surveyed patients with cancer-associated VTE found that most patients did not find the LMWH regimen to be difficult to use, distressing, or inconvenient, and that preference for oral medication versus injection was of moderate importance.[35,50–52]

Challenges to using DOACs to treat cancer-associated VTE are mostly related to safe administration of DOACs in patients with cancer. There is concern that the patient selection criteria used in the prospective randomized trials testing DOACs may have excluded a significant proportion of patients with cancer who need therapeutic anticoagulation in real world clinical settings. Supplemental eTable 3 summarizes exclusion criteria that may have impacted the eligibility of patients with cancer in these trials. Based on trial entry criteria, FDA prescribing information, and data on clinical/case-specific features that may increase the risk of adverse events, the NCCN Guidelines Panel developed a list of contraindications and warnings for each of the anticoagulants recommended for treatment of VTE in patients with cancer (see VTE-E 4 of 5, page 1294).

Some of the factors that could influence the efficacy and safety of DOACs include advanced age, weight/body mass index, gender, concomitant medications, kidney or liver function, chemotherapy-associated nausea/vomiting, and surgical resection of the proximal small bowel.[53–72] The recommended agents differ in the extent to which these variables impact drug clearance/absorption, and in the quality and quantity of safety data in special populations available to support dose adjustments. Likewise, anticoagulants vary widely in terms of the extent of information available on recommended dose adjustments based on the previously mentioned patient-specific factors.[73–75] There are ongoing debates among NCCN panel members and in the field on how to manage VTE patients with and without cancer in regards to drug–drug interactions, extremes of weight, compromised kidney and liver function, and previous small bowel resection. At present, it is recommended that alternative agents be considered in the event of major drug–drug interactions, severe renal or hepatic impairment, or small bowel resections until further data are developed to inform decision-making.

The NCCN Guidelines Panel discussed at length whether any subsets of patients with cancer are at particularly high risk of bleeding if treated with DOACs. Several studies have noted that patients with gastrointestinal (GI) and genitourinary (GU) cancers are increased risk for bleeding when treated with DOACs.[25,26] Subgroup analyses in the Hokusai VTE-Cancer trial found that patients with GI cancer at randomization had a significantly higher bleeding rate with LMWH plus edoxaban versus dalteparin monotherapy (13.2% [18/136] vs 2.4% [3/125]; P=.0224).[25] In addition, in the overall population (all cancer types), the trend toward higher rates of major bleeding with edoxaban was largely due to increases in the rate of GI and urogenital bleeds (patients with GI/GU bleeds, 4.8% vs 1.1% for edoxaban vs dalteparin arms). In the Select-D trial, analysis of bleeding rate according to primary tumor type showed that patients with esophageal or gastroesophageal cancer tended to experience more bleeding with rivaroxaban versus dalteparin (36% [4/11] versus 11% [1/19]), and in the overall population (all cancer types) the trend toward increased rates of major bleeding with rivaroxaban was due to higher rates of bleeds located in the GI and GU tracts (patients with GI/GU bleeds, 4.4% vs 2.0% for rivaroxaban vs dalteparin).[26] Hence the NCCN Guidelines list urinary or GI tract lesions, pathology, or instrumentation as relative contraindications to DOACs in patients with cancer.

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Conclusions

For patients with cancer-associated VTE for whom anticoagulation is appropriate, the NCCN Guidelines provide a list of recommended regimens. In addition to single-agent LMWH, edoxaban and rivaroxaban are considered preferred regimens by many panel members. Selection among agents should be based on the clinical setting (inpatient/outpatient), cost, ease of administration, monitoring, bleeding risk assessment, ability to reverse anticoagulation, and assessment of patient- and case-specific factors such as renal/hepatic function, potential for drug–drug interactions, GI/GU malignancies or instrumentation, and previous small bowel surgery. The NCCN Guidelines provide an agent-specific list of contraindications and warnings that should be considered when selecting treatment, and baseline laboratory testing needed to inform treatment and dose selection. Careful review of the prescribing information for each agent is also important for safe administration of these agents. For treatment in the outpatient setting, selection of a parenteral versus orally administered agent should include a discussion with the patient and their caregiver to ensure adherence to and completion of the prescribed treatment regimen.

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Posttest Questions

1. For a patient with stage IV breast cancer who develops a DVT and for whom anticoagulation is not contraindicated, which of the following single-agent options is a category 1 recommendation in the NCCN Guidelines for Cancer-Associated VTE?
   a. Unfractionated heparin
   b. Dalteparin
   c. Fondaparinux
   d. Apixaban
   e. Rivaroxaban

2. True or False: In the NCCN Guidelines for Cancer-Associated VTE, edoxaban is a recommended option for treatment of PE in patients with cancer, either as monotherapy or combination therapy with initial parenteral anticoagulant.

3. Which of the following patient- or case-specific features should be considered when selecting among anticoagulation options for treatment of VTE in patients with cancer?
   1. Kidney and liver function
   2. Body weight and BMI
   3. Patient age
   4. Tumor location
   5. Gastrointestinal side effects from concomitant cancer therapy

   There is only one correct answer:
   a. All of the above
   b. 1, 2, and 5
   c. All except 3