



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Cancer-Associated Venous Thromboembolic Disease

Version 3.2025 — November 6, 2025

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# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

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### [NCCN Cancer-Associated Venous Thromboembolic Disease Panel Members](#) [Summary of the Guidelines Updates](#)

#### **Venous Thromboembolism (VTE) Prophylaxis**

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- [VTE Prophylaxis Following Discharge and for At-Risk Ambulatory Patients With Cancer \(VTE-2\)](#)
- [Contraindications to VTE Prophylaxis \(VTE-A\)](#)
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#### **Workup and Treatment of VTE**

- [Acute Superficial Vein Thrombosis \(SVT-1\)](#)
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#### **Perioperative Management**

- [Perioperative Management of Anticoagulation and Antithrombotic Therapy \(PMA-1\)](#)
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- [Perioperative Management of Anticoagulation in Patients with Cancer \(PMA-C\)](#)

- [Abbreviations \(ABBR-1\)](#)

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**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

**NCCN Categories of Preference:**  
All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

#### **Heparin-Induced Thrombocytopenia (HIT)**

- [Workup and Management for Suspected HIT \(HIT-1\)](#)
- [HIT Pre-test Probability Models \(HIT-A\)](#)
- [Therapeutic Options for HIT \(HIT-B\)](#)

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# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

**Updates in Version 3.2025 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 2.2025 include:**

### MS-1

- The discussion section has been updated to reflect the changes in the algorithm.

**Updates in Version 2.2025 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2025 include:**

### VTE-D (2 of 7)

- Footnote d added to Apixaban dosing sub-bullet: After 6 months of therapy, consider lower dose apixaban (2.5 mg every 12 hours) after assessment of patient's risk for recurrent VTE and bleeding (Mahé I, et al. N Engl J Med 2025;392:1363-1373).

**Updates in Version 1.2025 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 2.2024 include:**

### Global Updates

- References have been updated throughout the guidelines.

### VTE-A

- Contraindications to Prophylactic Anticoagulation, bullet added: Pork product allergy (contraindication for LMWH and UFH)

### VTE-B (1 of 5)

- Enoxaparin
  - ▶ Dosing for BMI  $\geq 40$  kg/m<sup>2</sup>, options removed: BMI  $> 50$  kg/m<sup>2</sup>: Consider 60 mg SC every 12 hours OR 0.5 mg/kg actual body weight SC daily
- UFH
  - ▶ Dosing for Actual Body Weight 25-50 kg, option modified: Weight ~~<40~~ 50 kg: 2500 units SC every 8–12 hours
- Note added: § Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/> (Also for VTE-B 2 of 5, VTE-B 3 of 5, VTE-B 4 of 5, VTE-D 2 of 6, VTE-D 3 of 6, VTE-D 4 of 6, and as footnote c on HIT-B)
- Footnote a added: LMWH (enoxaparin and dalteparin) are preferred over UFH unless contraindicated (eg, poor renal function). (Also for VTE-B 3 of 5)
- Footnote f modified: "Dosing recommendations for patients weighing 25–~~40~~50 kg are included as guidance and based on expert opinion..." (Also for VTE-B 3 of 5)

### DVT-2

- Proximal lower extremity, contraindication to anticoagulation
  - ▶ No, bullet 3 modified: Consider *GCS compression therapy for symptom control* if the patient tolerates therapeutic anticoagulation

### PE-2

- Contraindication to anticoagulation, no, acute management using anticoagulation
  - ▶ Bullet 3, sub-bullet 1 modified: Systemic or catheter-directed thrombolysis or embolectomy for hemodynamically unstable PE in ~~patients with lower bleeding risk~~
- Footnote j modified: "...Consider echocardiography or CTA to assess right ventricular overload, NT-proBNP, ~~and~~ troponin, ~~and~~ lactate levels (Galić K, et al. Croat Med J 2018;59:149-155)..."

### SPVT-1

- Footnote a, bullet 2 modified: Abdominal mass/cancer (*hepatobiliary, luminal GI, pancreatic cancers*)

### VTE-D (2 of 7)

- Warfarin, bullet 3 added: The PT/INR can be prolonged by lupus inhibitors/anticoagulants, particularly point-of-care PT/INR. See Discussion for further discussion of management.

[Continued](#)

**UPDATES**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

Updates in Version 1.2025 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 2.2024 include:

### VTE-D (4 of 7)

- Agent modified: LMWH: *Dalteparin and enoxaparin*
  - ▶ LMWH, contraindications and warnings, bullet added: Pork product allergy
- DOACs, contraindications and warnings, bullet added: Antiphospholipid syndrome (APS)
- Footnote k modified: Although stage IV chronic kidney disease is not listed as a contraindication in the FDA-approved label for apixaban, the NCCN Panel acknowledges that there are ~~insufficient~~ *observational* data to support safe apixaban dosing in these patients, especially those who are on hemodialysis.
- Footnote l added: Warfarin is the preferred anticoagulant for most patients with APS. This is particularly true in patients with triple-positive APS or lupus inhibitors/anticoagulants but it has also been seen in patients with in single-and double-positive disease. DOACs should be used with caution (Knight JS, et al. BMJ. 2023;380:e069717).

### VTE-D (5 of 7)

- DOACs and GI Tract Surgery Considerations
  - ▶ Bullet 1 modified: DOACs are absorbed primarily in the stomach and proximal small bowel (with the exception of apixaban, which is also ~~partially~~ absorbed in the *distal small bowel and proximal* colon), so they may not be appropriate for patients who have had significant resections of these portions of the intestinal tract. The table below provides absorption guidance following GI surgical interventions based on available data.
  - ▶ Bullet 2 added: Retrospective cohort studies of patients who had bariatric and cancer GI surgery support the conclusion that apixaban drug levels are more likely to remain in the expected peak on treatment range than rivaroxaban after gastric or proximal small bowel resections. Dabigatran drug levels were below the peak on therapy range. Limited information is available for edoxaban but in the few patients studied, drug levels were in the expected peak on treatment range.
  - ▶ Bullet 3 modified: *Although uncertainty remains about the association of drug levels and clinical outcomes, we recommend considering drug levels in patients taking DOACs post-GI tract surgery.* ~~Due to limited data, consider checking a drug-specific anti-Xa level for Xa-inhibitors or a dabigatran level to ensure adequate absorption.~~

### VTE-G (1 of 3)

- Column 2, bullet added: Consider HIT and APS testing
- Subtherapeutic level, bullet 2 added: Consider drug-drug interactions, especially for DOACs
- Therapeutic level, consideration removed: Consider HIT and antiphospholipid syndrome (APS) testing
- Footnote b modified: Conditions associated with venous stasis such as vascular compression by tumors or lymphatic masses or stasis associated with IVC filters *can cause recurrent thrombosis despite therapeutic anticoagulation. Uncontrolled myeloproliferative neoplasms or paroxysmal nocturnal hemoglobinuria can also be responsible for this phenomenon. Relief of vascular stasis or treatment of MPN/PNH can reduce the risk of recurrence.*

### VTE-G (2 of 3)

- UFH, adjustment bullet 2 added: In patients with lupus inhibitor/anticoagulant or prolonged baseline aPTT, UFH anti-Xa level should be used for dose titration
- Warfarin, adjustment bullet 1 modified: Goal 2–3 *if baseline INR is normal*
- Warfarin, adjustment bullet 2 added: In patients with prolonged baseline PT/INR or lupus inhibitor/anticoagulant, target INR range should be confirmed with factor X activity or chromogenic factor X activity, respectively



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

Updates in Version 1.2025 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 2.2024 include:

### VTE-G (3 of 3)

- UFH, alternative anticoagulant, bullet 1 added: Confirm therapeutic aPTT with UFH anti-Xa level
- UFH, alternative anticoagulant, bullet 3 modified: Increase dose of UFH. *Use UFH anti-Xa levels to titrate UFH (in the event of recurrence in setting of subtherapeutic anti-Xa levels).*
- Warfarin, alternative anticoagulant, bullet 1 added: If factor X activity or chromogenic factor X activity is low despite therapeutic PT/INR, increase dose of warfarin and titrate to PT/INR range based upon therapeutic factor X or chromogenic factor X activity
- Apixaban, alternative anticoagulant, bullet modified: Switch to LMWH, *UFH*, fondaparinux (Also for dabigatran, edoxaban, rivaroxaban)
- Footnote f added: Ensure taking with largest meal of the day to promote absorption.

### VTE-I

- Contraindications to thrombolysis, absolute sub-bullet 1 modified: History of hemorrhagic stroke or ~~stroke of unknown origin~~ *intracranial hemorrhage*
- Indications for thrombolysis, bullet 2 modified: *Severely* symptomatic iliofemoral thrombosis (*select patients*)

### VTE-K (1 of 8)

- Bullet 3
  - ▶ Reversal of anticoagulation agent removed: Desmopressin (DDAVP)
  - ▶ Reversal of anticoagulation agent removed: Fresh frozen plasma (FFP)
- Precautions/additional considerations, bullet 1 modified: Protamine can cause anaphylaxis if administered too rapidly. *Protamine can also cause significant hypotension, bradycardia, and pulmonary hypertension, so monitor blood pressure, heart rate, and oxygenation closely during administration.*

### VTE-K (2 of 8)

- DTI, reversal of anticoagulation
  - ▶ Bullet 2, sub-bullet added: Monitor reversal with aPTT.
  - ▶ Bullet 2, sub-bullet removed: DDAVP 0.3 mcg/kg reduced bleeding in animal and ex-vivo models, and if used should be administered over 15–30 minutes.
- Argatroban, reversal of anticoagulation
  - ▶ Bullet 2, sub-bullet removed: DDAVP (0.3 mcg/kg) reduced bleeding in animal and ex-vivo models.
- Precautions/additional considerations, bullet 2 removed: Repeated doses (more than 3 or 4) of DDAVP are associated with tachyphylaxis and hyponatremia.

### VTE-K (4 of 8)

- Reversal of anticoagulation
  - ▶ Bullet 2, sub-bullet 2 removed: Alternative options may include: PCC
    - ◊ Sub-sub-bullet removed: aPCC 25–50 units/kg IV

[Continued](#)

UPDATES





# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

Updates in Version 1.2025 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 2.2024 include:

### VTE-K (6 of 8)

- Warfarin management of urgent surgery
  - ▶ Reversal of anticoagulation
    - ◊ Within 24 hours, bullet 3 modified: Repeat INR preoperative to determine need for supplemental FFP *PCC*
    - ◊ Within 48 hours, bullet 3 modified: Repeat INR at 24 and 48 hours to assess need for supplemental vitamin K1 or FFP *PCC*
  - ▶ Precautions/additional considerations
    - ◊ Bullet removed: Excessive intravascular volume (FFP)
    - ◊ Bullet removed: Transfusion-related acute lung injury (FFP)
    - ◊ Bullet removed: Pulmonary edema (FFP)
    - ◊ Bullet removed: Agglutination reactions/hemolysis due to blood-type incompatibility (FFP)
    - ◊ Bullet removed: Transfusion-associated graft-versus-host disease (if not irradiated FFP)
    - ◊ Bullet removed: Febrile nonhemolytic transfusion reactions (FFP)
- Note modified: ~~Prescribing information for coagulation factor Xa (recombinant), inactivated-zhzo. Lyophilized powder for solution for intravenous injection 2022. Available at: <https://www.fda.gov/media/143279/download>. Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/> (Also for VTE-K 7 of 8)~~

### PMA-A

- Table 1: Spinal injections moved from low to moderate risk.

### HIT-2

- Additional recommendations for patients with confirmed HIT
  - ▶ Bullet 3 added: Intravenous immunoglobulin has been shown to be effective in patients with refractory HIT as well as autoimmune HIT. It is also a useful treatment for patients at high risk of bleeding who have HIT.

### HIT-B

- Therapeutic option added: Intravenous Immunoglobulin (refractory HIT, autoimmune HIT, or patients at high risk of bleeding who have HIT)
  - ▶ Bullet 1 added: 1 g/kg IV daily x2



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## Cancer-Associated Venous Thromboembolic Disease

### INPATIENT VENOUS THROMBOEMBOLISM PROPHYLAXIS

#### POPULATION AT RISK

- Adults admitted for medical or surgical hospitalizations
- Diagnosis of cancer or clinical suspicion of cancer
- Providers are encouraged to assess venous thromboembolism (VTE) risk factors, risks and benefits of VTE prophylaxis, and to stress the importance of adherence to prevention programs<sup>a</sup>

#### WORKUP

- Initial Workup:**
- History and physical (H&P)
  - Complete blood count (CBC) with platelet count
  - Prothrombin time (PT)
  - Activated partial thromboplastin time (aPTT)
  - Liver and kidney function tests
  - VTE risk assessment

→ **Contraindication to anticoagulation<sup>b</sup>**

No →

**Pharmacologic prophylaxis**  
Prophylactic anticoagulation therapy (category 1); see [prophylactic anticoagulation options \(VTE-D\)](#)  
Consider preoperative dosing with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for high-risk surgery (eg, abdominal/pelvic surgery) ± intermittent pneumatic compression (IPC) device<sup>d,e,f</sup>

Yes →

**Mechanical prophylaxis<sup>e</sup>**  
IPC<sup>d,e</sup>

→ [VTE Prophylaxis Following Discharge and for At-Risk Ambulatory Patients with Cancer \(VTE-2\)](#)

<sup>a</sup> The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all patients hospitalized with cancer, excluding those with basal/squamous cell skin cancer. Although multiple risk assessment models (RAMs) have been developed for patients hospitalized for medical or surgical care, none of these RAMs have been validated in prospective management studies conducted in patients hospitalized with cancer.

<sup>b</sup> [Contraindications to VTE Prophylaxis \(VTE-A\)](#).

<sup>c</sup> Institutions are strongly encouraged to implement best practice programs to monitor provider and patient adherence to VTE prophylaxis.

<sup>d</sup> In contrast to graduated compression stockings (GCS), IPC significantly reduced deep vein thrombosis (DVT) and was associated with a lower risk of skin complications (CLOTS Trials Collaboration, et al. Lancet 2013;382:516-524; and CLOTS Trials Collaboration, et al. Lancet 2009;373:1958-1965).

<sup>e</sup> Most data come from patients admitted for surgery or stroke; this is an extrapolation to the medical population. See [Contraindications to VTE Prophylaxis \(VTE-A\)](#).

<sup>f</sup> Results from a randomized trial (including a limited number of patients with cancer) suggest that addition of mechanical prophylaxis to pharmacologic prophylaxis in patients who are critically ill may not reduce the incidence of DVT (Arabi YM, et al. N Engl J Med 2019;380:1305-1315).

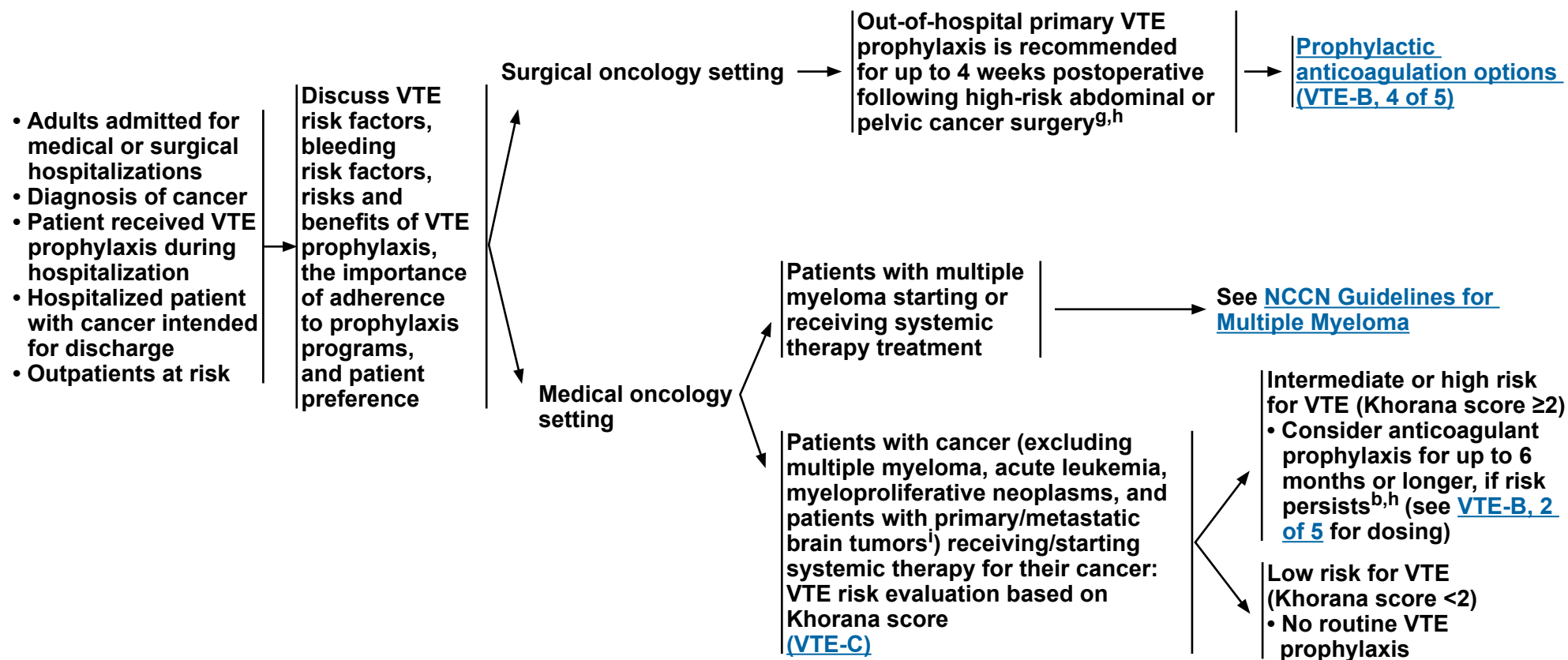
**Note: All recommendations are category 2A unless otherwise indicated.**





### VTE PROPHYLAXIS FOLLOWING DISCHARGE AND FOR AT-RISK AMBULATORY PATIENTS WITH CANCER

#### POPULATION AT RISK



<sup>b</sup> [Contraindications to VTE Prophylaxis \(VTE-A\)](#).

<sup>g</sup> Patients considered at high risk following abdominal/pelvic cancer surgery include patients undergoing surgery for gastrointestinal (GI) malignancies, patients with a previous history of VTE, anesthesia time >2 hours, bed rest ≥4 days, advanced-stage disease, and patient age >60 years.

<sup>h</sup> Patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with direct oral anticoagulants (DOACs).

<sup>i</sup> Patients receiving hormonal therapy were excluded from the AVERT but not the CASSINI trial.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### CONTRAINDICATIONS TO VTE PROPHYLAXIS<sup>a</sup>

#### Contraindications to Prophylactic Anticoagulation

- Active bleeding
- Thrombocytopenia (platelet count <50,000/μL or clinical judgment)<sup>b</sup>
- Underlying hemorrhagic coagulopathy (eg, abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (eg, hemophilia, von Willebrand disease)
- Indwelling neuraxial catheters (contraindication for apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban, or enoxaparin dose exceeding 40 mg daily)
- Neuraxial anesthesia/lumbar puncture<sup>c,d</sup>
- Interventional spine and pain procedures<sup>1</sup>
- Current or previous heparin-induced thrombocytopenia (HIT) (contraindication for LMWH and UFH)
- Pork product allergy (contraindication for LMWH and UFH)

#### Contraindications to Mechanical Prophylaxis

- Absolute
  - ▶ Acute DVT (unless on therapeutic anticoagulation)<sup>2</sup>
  - ▶ Severe arterial insufficiency (pertains to GCS only)
- Relative
  - ▶ Large hematoma
  - ▶ Skin ulcerations or wounds<sup>e</sup>
  - ▶ Mild arterial insufficiency (pertains to GCS only)
  - ▶ Peripheral neuropathy (pertains to GCS only)

<sup>1</sup> Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med* 2015;40:182-212.

<sup>2</sup> Rabe E, Partsch H, Morrison N, et al. Risks and contraindications of medical compression treatment - A critical reappraisal. An international consensus statement. *Phlebology* 2020;35:447-460.

<sup>a</sup> For agent-specific contraindications, see [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

<sup>b</sup> For patients at high risk, prophylactic anticoagulation may be appropriate even if platelet count is as low as 25,000/μL. See [Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia \(VTE-F\)](#).

<sup>c</sup> Refer to institutional-specific anesthesia practice guidelines, if available. Twice-daily prophylactic dose UFH (5000 units every 12 h) and once-daily LMWH (eg, enoxaparin 40 mg once daily) may be used with neuraxial anesthesia. Twice-daily prophylactic dose LMWH (eg, enoxaparin 30 mg every 12 h), prophylactic dose fondaparinux (2.5 mg daily), and therapeutic dose anticoagulation should be used with extreme caution with neuraxial anesthesia. The safety of thrice-daily prophylactic dose UFH in conjunction with neuraxial anesthesia has not been established (Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines [Third Edition]. *Reg Anesth Pain Med* 2010;35:64-101).

<sup>d</sup> Timing of LMWH: For LMWH, placement or removal of a neuraxial catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of DVT. Longer delays (24 h) are appropriate to consider for patients receiving therapeutic doses of LMWH. A post-procedure dose of LMWH should usually be given no sooner than 4 hours after catheter removal (FDA Drug Safety Communications. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on LMWH. November 6, 2013: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM373735.pdf>). In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.

<sup>e</sup> Skin ulcerations and wounds are more common with the use of GCS.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### VTE PROPHYLAXIS OPTIONS: MEDICAL ONCOLOGY INPATIENTS (VTE-1)<sup>a,b</sup>

Agent <sup>§</sup>	Standard Dosing <sup>c,d</sup>	Renal Dose	Dosing for Body Mass Index (BMI) ≥40 kg/m <sup>2</sup> <sup>e</sup>	Dosing for Actual Body Weight 25–50 kg <sup>f</sup>
Dalteparin <sup>1-6</sup>	5000 units SC daily (category 1)	Avoid if estimated creatinine clearance (CrCl) <30 mL/min	Consider 7500 units SC daily OR 5000 units SC every 12 hours OR 40–75 units/kg SC daily	Consider 2500 units SC daily OR 100 units/kg SC daily
Enoxaparin <sup>2-4,7-11</sup>	40 mg SC daily (category 1)	Recommend 30 mg SC daily if CrCl <30 mL/min	BMI >40 kg/m <sup>2</sup> : Consider 40 mg SC every 12 hours OR 0.5 mg/kg actual body weight SC daily	Actual body weight 25–40 kg: Consider 20 mg SC daily <sup>g</sup> (avoid if CrCl <30 mL/min)  Actual body weight 41–50 kg: Consider 30 mg SC daily <sup>g</sup> (avoid if CrCl <30 mL/min)
Fondaparinux <sup>3,12-14</sup>	2.5 mg SC daily (category 1)	Caution if CrCl 30–49 mL/min Avoid if CrCl <30 mL/min	Consider 5 mg SC daily	Contraindicated for body weight <50 kg
UFH <sup>13,15,16</sup>	5000 units SC every 8–12 hours	Same as standard dose	Consider 7500 units SC every 8 hours	Weight <50 kg: 2500 units SC every 8–12 hours <sup>g</sup>

§ Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

<sup>a</sup> LMWH (enoxaparin and dalteparin) are preferred over UFH unless contraindicated (eg, poor renal function).

<sup>b</sup> Patients hospitalized for medical oncology care can continue apixaban/rivaroxaban prophylaxis if either option is already being used in the outpatient setting; however, apixaban/rivaroxaban should not be initiated in the hospital. Apixaban/rivaroxaban prophylaxis is also an option for patients with a history of HIT, for whom a heparin-based regimen is not feasible.

<sup>c</sup> Recommendations derived from patients hospitalized with medical illness, including those with cancer.

<sup>d</sup> Thromboprophylaxis for duration of hospital stay or 6 to 14 days or until the patient is fully ambulatory.

<sup>e</sup> Limited to no data available to support recommendations. Recommended doses are derived from non-oncology populations.

<sup>f</sup> Dosing recommendations for patients weighing 25–50 kg are included as guidance and based on expert opinion. Available data suggest administration of standard VTE prophylaxis doses to patients in this weight range results in over-exposure and increased bleeding, but there are very limited data available to inform dose reduction strategies. Buckheit D, et al. Clin Appl Thromb Hemost 2021;27:1-6; Sebaaly J, et al. Ann Pharmacother 2018;52:898-909.

<sup>g</sup> Consider laboratory monitoring. If dose escalation or de-escalation is required twice, consult with hematology or a clinical anticoagulation pharmacy specialist. Singer GA, et al. J Trauma Acute Care Surg 2016;81:1101-1108.

**Note: All recommendations are category 2A unless otherwise indicated.**

[References on VTE-B 5 of 5](#)



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### VTE PROPHYLAXIS OPTIONS: AMBULATORY MEDICAL ONCOLOGY PATIENTS AND PATIENTS POST-MEDICAL ONCOLOGY DISCHARGE [\(VTE-2\)](#)<sup>h,i</sup>

Agent <sup>§</sup>	Standard Dosing	Renal Dose	Other Dose Modifications
Apixaban <sup>j,17</sup>	2.5 mg PO twice daily	Caution if CrCl <30 mL/min <sup>k</sup>	Avoid if platelet count <50,000/μL Avoid if weight <40 kg
Rivaroxaban <sup>l,18</sup>	10 mg PO once daily	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL
Dalteparin <sup>m,19</sup>	200 units/kg SC daily x 1 month, then 150 units/kg SC daily x 2 months	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL
Enoxaparin <sup>m,20</sup>	1 mg/kg SC daily x 3 months, then 40 mg SC daily	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL

<sup>§</sup> Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

<sup>h</sup> Recommendations derived from clinical trials of ambulatory patients with cancer with high thrombosis risk (>18 years, Khorana VTE Risk Score of ≥2, initiating new course of chemotherapy) and are not included in product labeling. Prophylaxis duration should be 6 months or longer if risk persists.

<sup>i</sup> For recommendations for thromboprophylaxis in patients with multiple myeloma, see [NCCN Guidelines for Multiple Myeloma](#).

<sup>j</sup> Apixaban is absorbed in the stomach, proximal small bowel, and colon. Patients who have had significant resections of these portions of the intestinal tract may be at risk for suboptimal absorption. See [VTE-D](#).

<sup>k</sup> Patients with CrCl <30 mL/min were excluded from VTE prophylaxis studies. Due to limited data in this population, use with caution. May consider use in extenuating circumstances such as HIT.

<sup>l</sup> DOACs are absorbed primarily in the stomach and proximal small bowel, so they may not be appropriate for patients who have had significant resections of these portions of the intestinal tract. See [VTE-D](#).

<sup>m</sup> Data support the use of prophylactic dalteparin and enoxaparin for patients with advanced unresectable and metastatic pancreatic cancer (Maraveyas A, et al. Eur J Cancer 2012;48:1283-1292; Pelzer U, et al. J Clin Oncol 2015;33:2028-2034).

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**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### VTE PROPHYLAXIS OPTIONS: SURGICAL ONCOLOGY INPATIENTS (VTE-1)<sup>a</sup>

Agent <sup>§</sup>	Standard Dosing <sup>n,o</sup>	Renal Dose	Dosing for BMI ≥40 kg/m <sup>2</sup> <sup>e</sup>	Dosing for Actual Body Weight 25–50 kg <sup>f</sup>
Dalteparin <sup>1-3</sup>	5000 units SC the evening prior to surgery, then 5000 units SC daily OR 2500 units SC 1–2 hours prior to surgery and 2500 units SC 12 hours later, then 5000 units SC daily beginning postoperative day (POD) 1	Avoid if CrCl <30 mL/min	Consider 7500 units SC daily OR 5000 units SC every 12 hours OR 40–75 units/kg SC daily	No dose adjustment available
Enoxaparin <sup>2,3,7</sup>	40 mg SC 2–12 hours prior to surgery, then once daily postoperatively <sup>21,22</sup>	Recommend 30 mg SC daily if CrCl <30 mL/min	Consider 40 mg SC every 12 hours OR 0.5 mg/kg SC daily	Actual body weight 25–40 kg: Consider 20 mg SC daily <sup>9</sup> (avoid if CrCl <30 mL/min) OR Actual body weight 41–50 kg: Consider 30 mg SC daily <sup>9</sup> (avoid if CrCl <30 mL/min)
Fondaparinux <sup>2,3,7,12</sup>	2.5 mg SC daily no earlier than 6–8 hours postoperatively Avoid in patients weighing <50 kg	Caution if CrCl 30–49 mL/min Avoid if CrCl <30 mL/min	Consider 5 mg SC daily	No dose adjustment available
UFH <sup>19,20,23</sup>	5000 units SC 2 hours prior to surgery, then 5000 units SC every 8 hours through POD1	Same as standard dose	Consider 7500 units SC every 8 hours postoperatively	Weight <50 kg: 2500 units SC every 8–12 hours <sup>9</sup>
Apixaban <sup>j,p,24</sup>	Apixaban 2.5 mg PO every 12 hours starting POD 1–7 depending upon hemostasis. Recommend UFH or LMWH in prophylactic doses starting preoperation and continuing postoperation until judged safe to switch to apixaban	Caution if CrCl <30 mL/min <sup>k</sup>	No dose adjustment available	No dose adjustment available
Rivaroxaban <sup>q,25</sup>	LMWH prophylaxis in standard doses for first week, then rivaroxaban 10 mg daily for 3 additional weeks	Avoid if CrCl <30 mL/min	No dose adjustment available	No dose adjustment available

§ Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

<sup>a</sup> LMWH (enoxaparin and dalteparin) are preferred over UFH unless contraindicated (eg, poor renal function).

<sup>e</sup> Limited to no data available to support recommendations. Recommended doses are derived from non-oncology populations.

<sup>f</sup> Dosing recommendations for patients weighing 25–50 kg are included as guidance and based on expert opinion. Available data suggest administration of standard VTE prophylaxis doses to patients in this weight range results in over-exposure and increased bleeding, but there are very limited data available to inform dose reduction strategies. Buckheit D, et al. Clin Appl Thromb Hemost 2021;27:1-6; Sebaaly J, et al. Ann Pharmacother 2018;52:898-909.

<sup>g</sup> Consider laboratory monitoring. If dose escalation or de-escalation is required twice, consult with hematology or a clinical anticoagulation pharmacy specialist. Singer GA, et al. J Trauma Acute Care Surg 2016;81:1101-1108.

<sup>j</sup> Apixaban is absorbed in the stomach, proximal small bowel, and colon. Patients who have had significant resections of these portions of the intestinal tract may be at risk for suboptimal absorption. See [VTE-D](#).

<sup>k</sup> Patients with CrCl <30 mL/min were excluded from VTE prophylaxis studies. Due to limited data in this population, use with caution. May consider use in extenuating circumstances such as HIT.

<sup>n</sup> Recommendations derived from patients undergoing planned, elective, open abdominal, or pelvic surgery for malignancy (operating room [OR] time >45 minutes, age >40 years).

<sup>o</sup> Thromboprophylaxis for 7 to 10 days or until the patient is fully ambulatory.

<sup>p</sup> Only applies to patients with gynecologic cancers. Apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed. Duration of prophylaxis was 28 days.

<sup>q</sup> Only applies to patients after laparoscopic surgery for colorectal cancer.

**Note: All recommendations are category 2A unless otherwise indicated.**

[References on VTE-B 5 of 5](#)



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### VTE PROPHYLAXIS OPTIONS: POST-DISCHARGE PROPHYLAXIS FOR SURGICAL ONCOLOGY PATIENTS [\(VTE-2\)](#)

Agent <sup>§</sup>	Standard Dosing <sup>n</sup>	Renal Dose	Other Dose Modifications
Apixaban <sup>j,p,24</sup>	2.5 mg PO every 12 hours x 28 days	Caution if CrCl <30 mL/min <sup>k</sup>	Avoid if platelet count <50,000/μL Avoid if weight <40 kg
Rivaroxaban <sup>q,25</sup>	10 mg daily for 21 days <sup>r</sup>	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL
Dalteparin <sup>s,20,26,27</sup>	5000 units SC daily x 28 days	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL
Enoxaparin <sup>s,21,26,28,29</sup>	40 mg SC daily x 28 days	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL

<sup>§</sup> Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

<sup>j</sup> Apixaban is absorbed in the stomach, proximal small bowel, and colon. Patients who have had significant resections of these portions of the intestinal tract may be at risk for suboptimal absorption. See [VTE-D](#).

<sup>k</sup> Patients with CrCl <30 mL/min were excluded from VTE prophylaxis studies. Due to limited data in this population, use with caution. May consider use in extenuating circumstances such as HIT.

<sup>n</sup> Recommendations derived from patients undergoing planned, elective, open abdominal, and pelvic surgery for malignancy (OR time >45 minutes, age ≥40 years).

<sup>p</sup> Only applies to patients with gynecologic cancers. Apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed. Duration of prophylaxis was 28 days.

<sup>q</sup> Only applies to patients after laparoscopic surgery for colorectal cancer.

<sup>r</sup> Start rivaroxaban after 1 week of standard-dose LMWH (enoxaparin 40 mg SC daily or dalteparin 5000 units SC daily).

<sup>s</sup> For patients at high risk following abdominal and pelvic surgery (previous VTE, bed rest ≥4 days, OR time >2 hours, advanced-stage disease, or age ≥60 years), 4 weeks of thromboprophylaxis is recommended.<sup>16,18</sup>

[References on VTE-B 5 of 5](#)

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### VTE PROPHYLAXIS OPTIONS REFERENCES

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**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### VTE RISK ASSESSMENT IN OUTPATIENTS WITH CANCER

#### Khorana Predictive Model for Chemotherapy-Associated VTE<sup>a,b</sup>

<u>Patient Characteristic</u>	<u>Risk Score</u>	
• Site of primary cancer		
▶ Very high risk (stomach, pancreas)	2	
▶ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1	
• Prechemotherapy platelet count 350 x 10 <sup>9</sup> /L or higher	1	
• Hemoglobin level less than 10 g/dL or use of red cell growth factors	1	
• Prechemotherapy leukocyte count higher than 11 x 10 <sup>9</sup> /L	1	
• BMI 35 kg/m <sup>2</sup> or higher	1	
<u>Total Score</u>	<u>Risk Category</u>	<u>Risk of Symptomatic VTE<sup>1</sup></u>
0	Low	0.3–1.5%
1, 2	Intermediate	2.0–4.8%
3 or higher	High	6.7–12.9%

<sup>1</sup> Khorana AA. Cancer and Coagulation. Am J Hematol 2012;87 Supp 1:S82-87.

<sup>a</sup> Reproduced and adapted with permission from Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-4907.

<sup>b</sup> The Khorana Predictive Model is the most validated RAM. Several other RAMs have been published including the Protecht model, the CONKO score, the ONKOTEV score, the TiC-Onco score, and the COMPASS-CAT model. The utility of these models in the oncology population needs to be further evaluated in prospective, randomized trials.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Acute Superficial Vein Thrombosis

### DIAGNOSIS

Clinical suspicion of superficial vein thrombosis (SVT):

- Pain, erythema, and tenderness involving a superficial vein in the extremity

### WORKUP/IMAGING

- Comprehensive medical H&P
- CBC with platelet count
- PT, aPTT
- Liver and kidney function tests
- Consider venous ultrasound (US) based on clinical judgment

### IMAGING FINDINGS

Upper extremity SVT (median, basilic, and/or cephalic veins)

If peripheral catheter is related and catheter no longer indicated, remove catheter<sup>a</sup>

Lower extremity SVT (great and small saphenous veins)

### SVT TREATMENT

- Use symptomatic treatment<sup>b</sup> and monitor for progression
- If progression symptomatically or on imaging, prophylactic dose anticoagulation is recommended<sup>c</sup>
- Consider therapeutic dose anticoagulation<sup>d</sup> if the clot is in close proximity<sup>e</sup> to the deep venous system

- Prophylactic dose anticoagulation<sup>c</sup> for at least 6 weeks if:
  - ▶ SVT >5 cm in length<sup>f</sup>
  - ▶ SVT extends above knee<sup>f</sup>
- Therapeutic dose anticoagulation<sup>d</sup> for at least 3 months if SVT is within 3 cm of the saphenofemoral junction
- Consider repeat US in 7–10 days if SVT <5 cm in length or below knee. If repeat US shows progression, consider anticoagulation<sup>c</sup>

<sup>a</sup> For patients with SVT associated with a peripherally inserted central catheter (PICC) line, catheter removal may not be necessary, especially if the patient is treated with anticoagulation and/or symptoms resolve.

<sup>b</sup> Symptomatic treatment includes warm compresses, nonsteroidal anti-inflammatory drugs (NSAIDs), and elevation.

<sup>c</sup> Prophylactic dose anticoagulation with rivaroxaban 10 mg PO daily and fondaparinux 2.5 mg SC daily have been shown to be effective in some studies that included a limited number of patients with cancer (Beyer-Westendorf J, et al. Lancet Haematol 2017;4:e105-e113). Therapeutic dosing may be used at the clinician's discretion. See [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

<sup>d</sup> [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

<sup>e</sup> Close proximity is defined as within approximately 3 cm.

<sup>f</sup> If SVT is within 3 cm from the saphenofemoral junction, treat with therapeutic dose anticoagulation. See [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Acute Deep Vein Thrombosis

### DIAGNOSIS

Clinical suspicion of DVT:

- Swelling of unilateral extremity
- Heaviness in extremity
- Pain in extremity
- Unexplained persistent calf cramping
- Swelling in face, neck, or supraclavicular space
- Catheter dysfunction (If catheter is present, see [Catheter-Related DVT \[DVT-3\]](#))

### WORKUP/IMAGING

- Comprehensive medical H&P
- CBC with platelet count
- PT, aPTT ± fibrinogen
- Liver and kidney function tests
- Venous US<sup>a</sup>

### IMAGING FINDINGS

Positive for DVT

Negative or indeterminate

Continued clinical suspicion of DVT

Yes

No

### ADDITIONAL IMAGING

- Venous imaging:
- Repeat venous US
  - CT venogram (CTV) with contrast
  - Magnetic resonance venogram (MRV) with contrast

### DVT TREATMENT

[Treatment \(DVT-2\)](#)

Positive for DVT

Negative

- Reassurance
- Evaluate for other causes

Incidental DVT

- If not already performed:
- Comprehensive medical H&P
  - CBC with platelet count
  - PT, aPTT ± fibrinogen
  - Liver and kidney function tests
  - Venous US<sup>b</sup>

[Treatment \(DVT-2\)](#)

<sup>a</sup> In cases with high suspicion of DVT and no contraindications, consider initiating early anticoagulation while awaiting imaging results.  
<sup>b</sup> If initial imaging results are inconclusive, consider venous US to confirm diagnosis.

Note: All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 3.2025

## Acute Deep Vein Thrombosis

### DVT LOCATION

### DVT: TREATMENT

**PROXIMAL LOWER EXTREMITY**  
• Pelvic/iliac/inferior vena cava (IVC)  
• Femoral/popliteal

Contraindication to anticoagulation<sup>c</sup>

No →

- Anticoagulation<sup>d,e</sup>
- Consider catheter-directed therapy (pharmacomechanical thrombolysis or mechanical thrombectomy) in appropriate candidates<sup>f,g,h</sup>
- Consider compression therapy for symptom control if the patient tolerates therapeutic anticoagulation<sup>i</sup>

Yes →

IVC filter (retrievable filter preferred)

Contraindication<sup>c</sup> persists or is likely to recur

No →

- Anticoagulation<sup>d,e</sup>
- Filter removal<sup>j</sup>

Yes →

Re-evaluate regularly for change in status

**DISTAL LOWER EXTREMITY**  
• Peroneal, anterior and posterior tibial, and muscular (soleus and gastrocnemius)

Contraindication to anticoagulation<sup>c</sup>

No →

Anticoagulation<sup>d,e</sup>

Yes →

Follow-up with serial US

Progression to proximal vein

See Pelvic/iliac/IVC and Femoral/popliteal pathway above

Local progression (but not to proximal deep vein)

No progression

Continue to follow as clinically indicated

**UPPER LIMB/CHEST**  
• Brachiocephalic, subclavian, axillary, internal jugular, brachial  
• Superior vena cava (SVC)

Contraindication to anticoagulation<sup>c</sup>

No →

- Anticoagulation<sup>d,e</sup>
- Consider catheter-directed therapy (pharmacomechanical thrombolysis or mechanical thrombectomy) in appropriate candidates<sup>f,g,h</sup>

Yes →

Follow until contraindication is resolved or progression of DVT

Re-evaluate for risk/benefit of anticoagulation<sup>k</sup>

Note: All recommendations are category 2A unless otherwise indicated.

[Footnotes on DVT-2A](#)



# NCCN Guidelines Version 3.2025

## Acute Deep Vein Thrombosis

### FOOTNOTES

- <sup>c</sup> [Contraindications to Therapeutic Anticoagulation \(VTE-E\)](#) and [Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia \(VTE-F\)](#).
- <sup>d</sup> [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).
- <sup>e</sup> See [Progression or New Thrombosis on Therapeutic Anticoagulation \(VTE-G\)](#), if extension of VTE or new VTE while on recommended anticoagulation therapy.
- <sup>f</sup> Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues ([VTE-H](#)). Appropriate candidates may include: patients at risk of limb loss (eg, phlegmasia cerulea dolens), patients with central thrombus propagation despite anticoagulation, and those with moderate to severely symptomatic proximal DVT. Candidates with high bleeding risk or contraindication to fibrinolytic may be candidates for percutaneous mechanical thrombectomy.
- <sup>g</sup> [Contraindications to Thrombolysis and Indications for Thrombolysis \(VTE-I\)](#).
- <sup>h</sup> Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.
- <sup>i</sup> GCS did not reduce the incidence of post-thrombotic syndrome (PTS) in a double-blind randomized trial (Kahn SR, et al. Lancet 2014;383:880-888).
- <sup>j</sup> Recommend IVC filter removal, if tolerating anticoagulation.
- <sup>k</sup> [Elements for Consideration in Decision Not to Treat \(VTE-J\)](#).

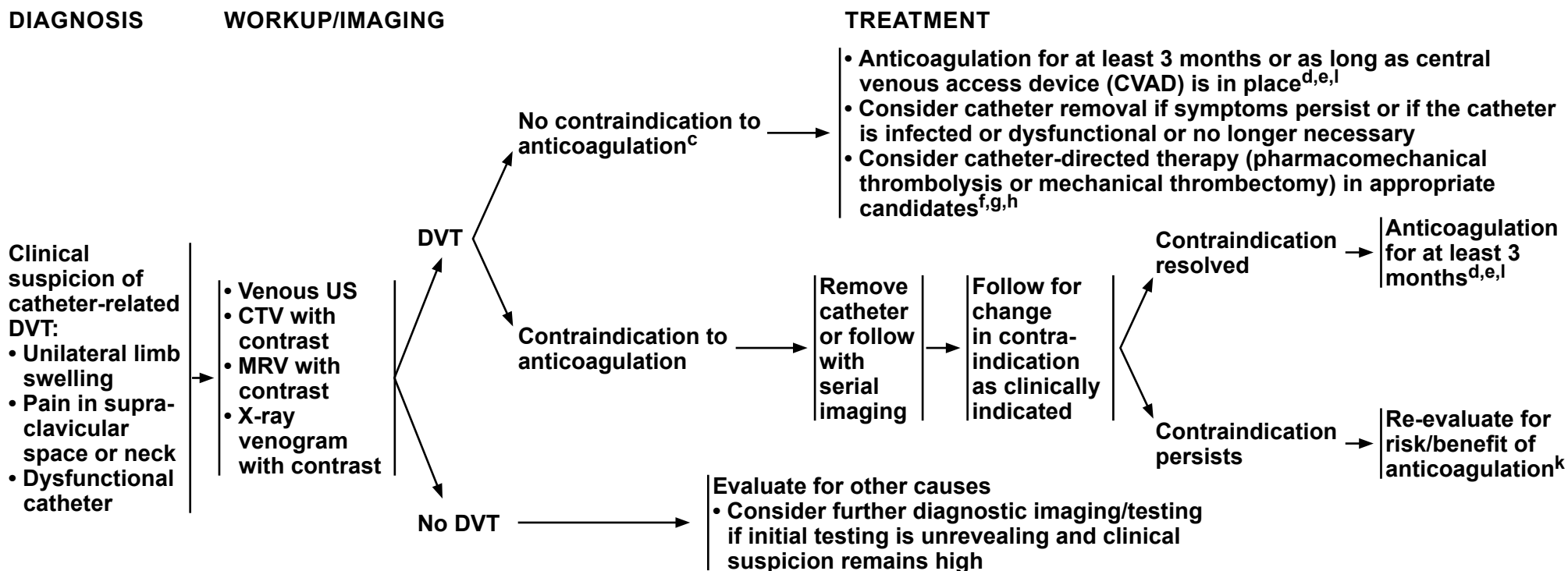
**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Acute Deep Vein Thrombosis

### CATHETER-RELATED DVT: DIAGNOSIS AND TREATMENT



<sup>c</sup> [Contraindications to Therapeutic Anticoagulation \(VTE-E\)](#) and [Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia \(VTE-F\)](#).

<sup>d</sup> [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

<sup>e</sup> See [Progression or New Thrombosis on Therapeutic Anticoagulation \(VTE-G\)](#), if extension of VTE or new VTE while on recommended anticoagulation therapy.

<sup>f</sup> Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues ([VTE-H](#)). Appropriate candidates may include: patients at risk of limb loss (eg, phlegmasia cerulea dolens), patients with central thrombus propagation despite anticoagulation, and those with moderate to severely symptomatic proximal DVT. Candidates with high bleeding risk or contraindication to fibrinolytic may be candidates for percutaneous mechanical thrombectomy.

<sup>g</sup> [Contraindications to Thrombolysis and Indications for Thrombolysis \(VTE-I\)](#).

<sup>h</sup> Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.

<sup>k</sup> [Elements for Consideration in Decision Not to Treat \(VTE-J\)](#).

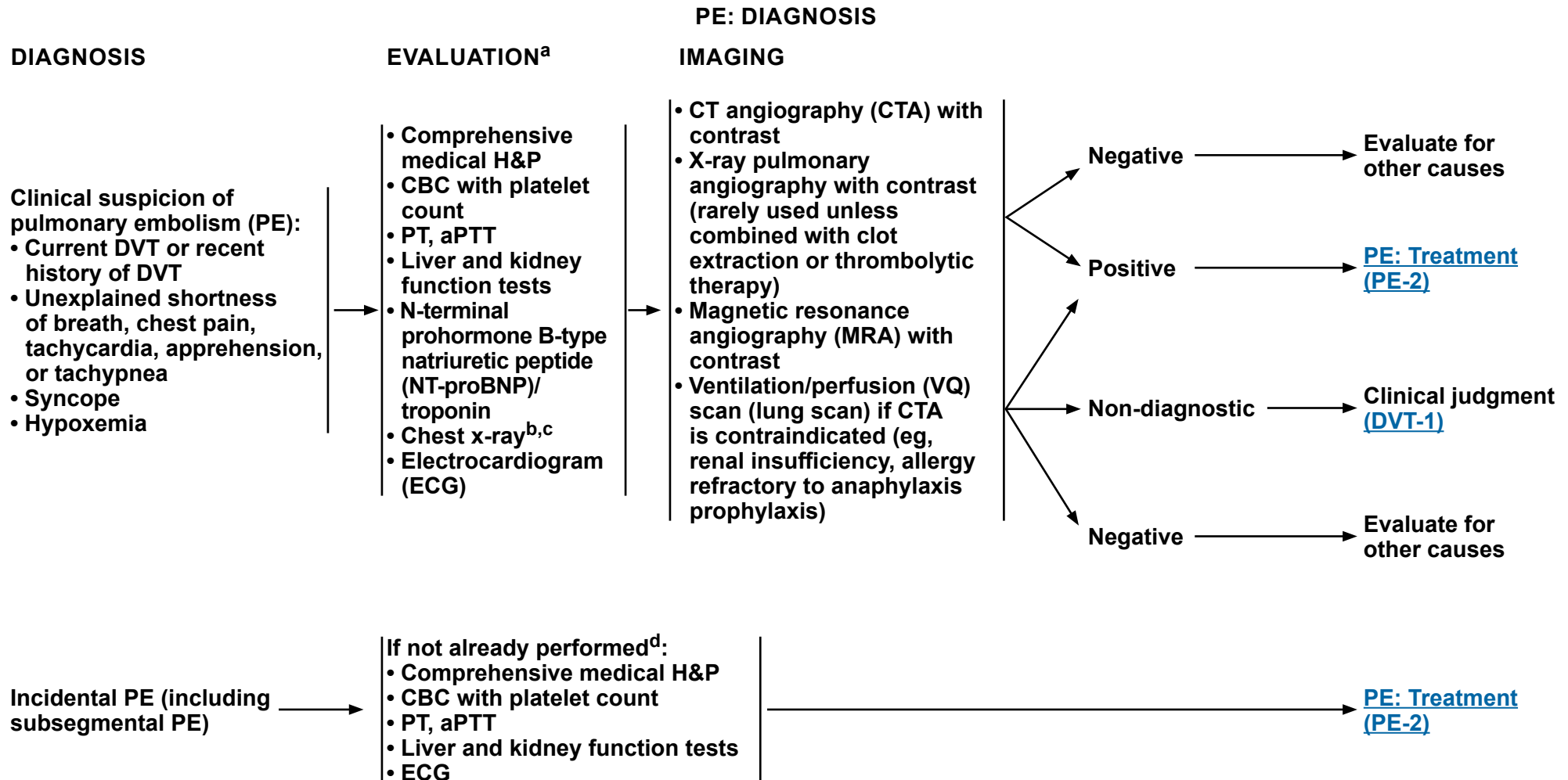
<sup>l</sup> Anticoagulation without catheter removal is the preferred option for initial treatment, even for patients with symptomatic DVT, provided that the catheter is necessary, functional, and free of infection. There is very little clinical evidence regarding the appropriate duration of anticoagulation. The recommended duration of anticoagulation depends on tolerance of anticoagulation, response to anticoagulation, and catheter status. Consider longer duration anticoagulation in patients with catheters with poor flow, persistent symptoms, or unresolved thrombus. Consider shorter duration of anticoagulation if clot or symptoms resolve in response to anticoagulation and/or catheter removal.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Acute Pulmonary Embolism



<sup>a</sup> D-dimer has limited utility in patients with cancer.

<sup>b</sup> In cases with high suspicion of PE and no contraindications, consider initiating early anticoagulation while waiting for imaging results.

<sup>c</sup> Chest x-ray may not be necessary if CTA is planned.

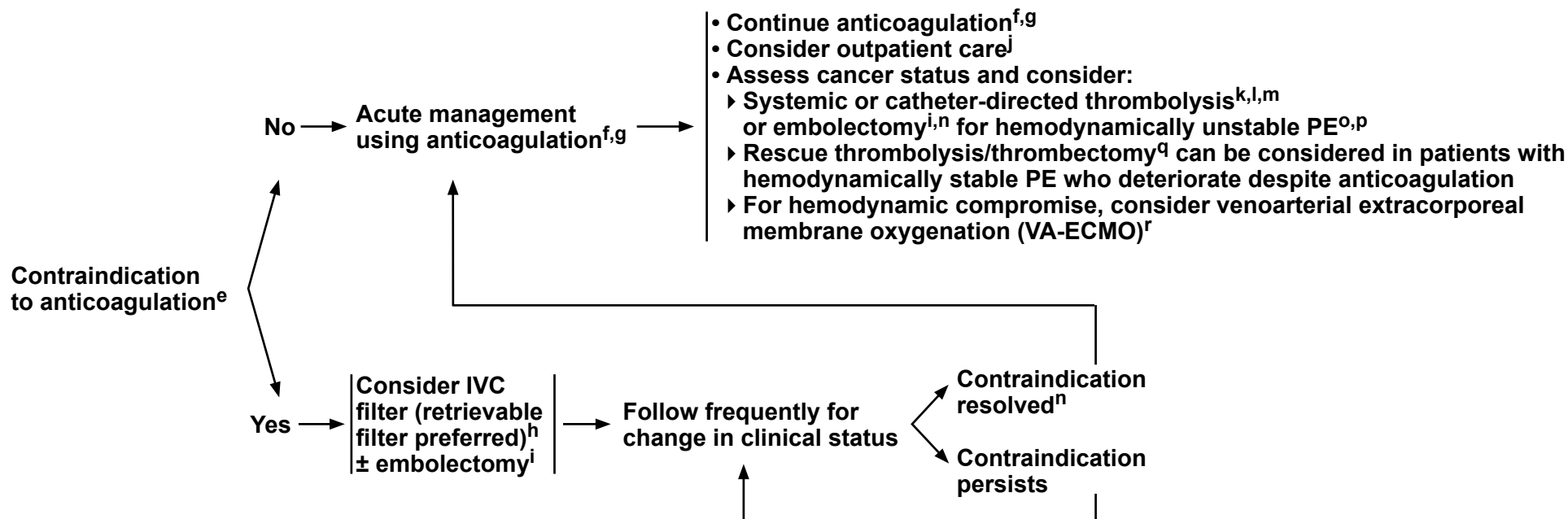
<sup>d</sup> Repeat imaging and diagnostic studies are not routinely needed in patients with incidental PE. Consider outpatient care for these patients.

**Note: All recommendations are category 2A unless otherwise indicated.**

# NCCN Guidelines Version 3.2025

## Acute Pulmonary Embolism

### PE: TREATMENT



- Continue anticoagulation<sup>f,g</sup>
- Consider outpatient care<sup>j</sup>
- Assess cancer status and consider:
  - Systemic or catheter-directed thrombolysis<sup>k,l,m</sup> or embolectomy<sup>i,n</sup> for hemodynamically unstable PE<sup>o,p</sup>
  - Rescue thrombolysis/thrombectomy<sup>q</sup> can be considered in patients with hemodynamically stable PE who deteriorate despite anticoagulation
  - For hemodynamic compromise, consider venoarterial extracorporeal membrane oxygenation (VA-ECMO)<sup>r</sup>

<sup>e</sup> [Contraindications to Therapeutic Anticoagulation \(VTE-E\)](#) and [Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia \(VTE-F\)](#).

<sup>f</sup> [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

<sup>g</sup> See [Progression or New Thrombosis on Therapeutic Anticoagulation \(VTE-G\)](#), if extension of VTE or new VTE while on recommended anticoagulation therapy.

<sup>h</sup> Consider filter placement if unable to treat with anticoagulation within 1 month of onset of symptomatic PE (Streiff MB, et al. J Thromb Thrombolysis 2016;41:32-67).

<sup>i</sup> Consider embolectomy for treatment of massive PE (category 2B).

<sup>j</sup> Patients at lower risk as identified by clinical, laboratory, and imaging assessment can be considered for outpatient care. Consider echocardiography or CTA to assess right ventricular overload, NT-proBNP, troponin, and lactate levels (Galić K, et al. Croat Med J 2018;59:149-155). Clinical judgment is recommended for assessing risk in patients with PE based on a variety of clinical parameters. Signs of decompensation or life-threatening PE include: hypoxemia, hypotension, dyspnea, tachycardia, and tachypnea.

<sup>k</sup> [Elements for Consideration in Decision Not to Treat \(VTE-J\)](#).

<sup>l</sup> [Thrombolytic Agents \(VTE-H\)](#).

<sup>m</sup> [Contraindications to Thrombolysis and Indications for Thrombolysis \(VTE-I\)](#).

<sup>n</sup> Recommend IVC filter removal, if tolerating anticoagulation therapy.

<sup>o</sup> In randomized controlled trials, systemic or catheter-directed thrombolysis/thrombectomy has not been associated with a favorable risk-versus-benefit profile in patients with hemodynamically stable or submassive PE.

<sup>p</sup> Acute PE with sustained hypotension (systolic blood pressure <90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock). (Konstantinides SV, et al. Eur Heart J 2020;41:543-603).

<sup>q</sup> Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.

<sup>r</sup> Pasrija C, et al. Ann Thorac Surg 2018;105:498-504.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Splanchnic Vein Thrombosis

### SPLANCHNIC VEIN THROMBOSIS (SPVT): DIAGNOSIS

#### CLINICAL SUSPICION OF SPVT<sup>a</sup>

- Abdominal or mid-abdominal colicky pain
- Abdominal distention
- Rebound tenderness
- Guarding
- Fever
- Anorexia
- Nausea, vomiting
- Diarrhea
- Gastrointestinal (GI) bleeding
- Hepatomegaly
- Ascites

#### DIAGNOSTIC EVALUATION

##### History and physical

- Based on H&P, consider further diagnostic testing

##### Laboratory testing

- CBC with platelet count and differential
- PT, aPTT
- Basic metabolic profile
- Hepatic profile
- Serum lactate

##### Imaging<sup>b</sup>

- Abdominal duplex US
- CT abdomen/pelvis with contrast
- Abdominal MRI with contrast

Negative or indeterminate

Continued suspicion

No

Investigate other causes

Yes

Repeat imaging<sup>b</sup>

Positive

Treatment ([SPVT-2](#))

• Incidental SPVT

Treatment ([SPVT-2](#))<sup>c</sup>

<sup>a</sup> Risk factors relevant to cancer population for SPVT:

- Recent abdominal surgery (eg, splenectomy)
- Abdominal mass/cancer (hepatobiliary, luminal GI, pancreatic cancers)
- Pancreatitis
- Cirrhosis
- Exogenous estrogens
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Myeloproliferative neoplasms (MHN) associated with the *JAK2* V617F mutation (most common) or *CALR* mutation (rare)

<sup>b</sup> Consider local consultation with radiology to optimize imaging techniques/modality.

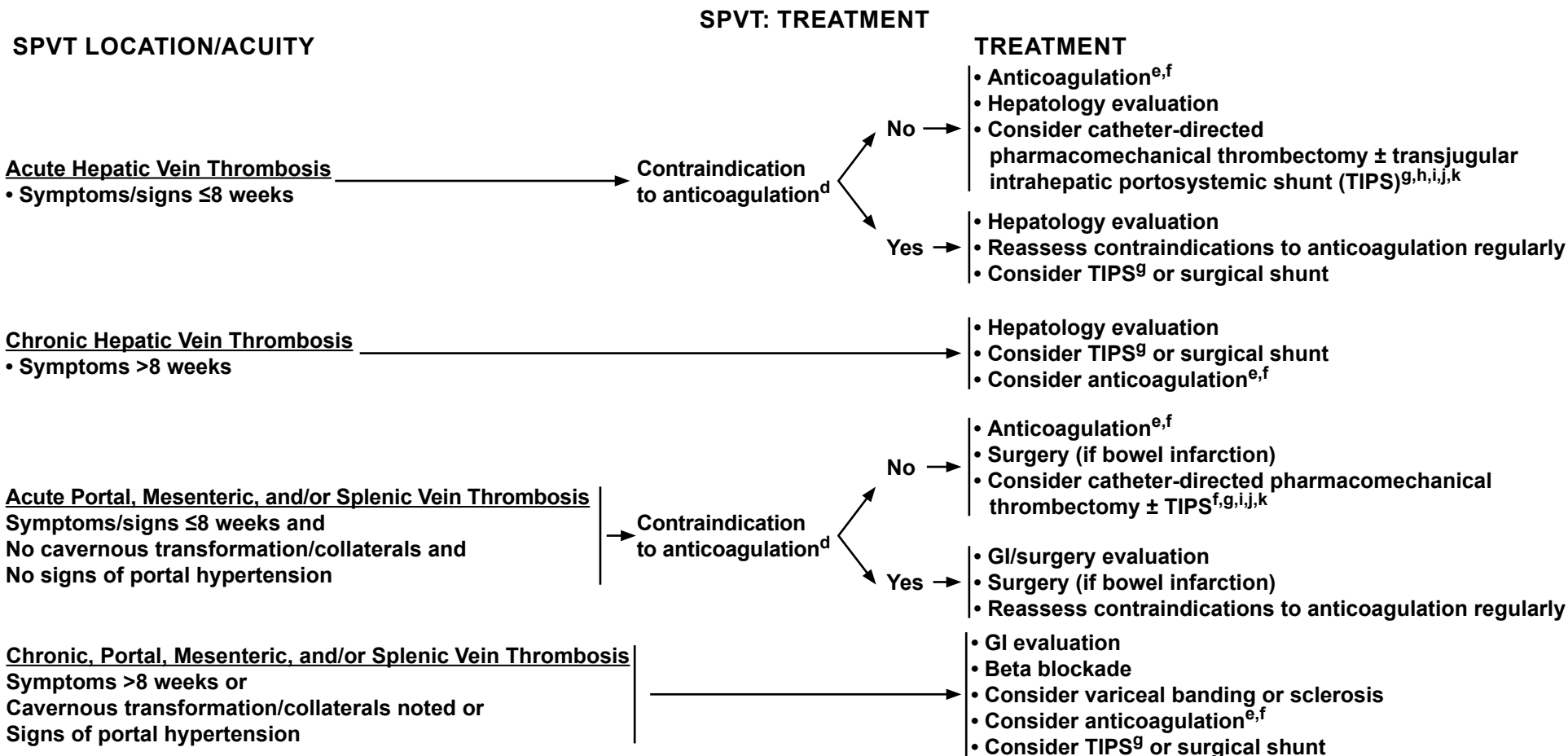
<sup>c</sup> For incidental SPVT, weigh the risks and benefits of anticoagulation therapy on an individual basis.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Splanchnic Vein Thrombosis



<sup>d</sup> [Contraindications to Therapeutic Anticoagulation \(VTE-E\)](#) and [Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia \(VTE-F\)](#).

<sup>e</sup> Weigh risks/benefits of anticoagulation, particularly for chronic thromboses. Duration of anticoagulation should be at least 6 months for triggered events (eg, postsurgical) and indefinite if active cancer, persistent thrombophilic state, or unprovoked thrombotic event.

<sup>f</sup> [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

<sup>g</sup> Consider TIPS as one of the management options for patients with SPVT and portal hypertension.

<sup>h</sup> If thrombectomy expertise is not available, consider consultation with a tertiary medical center.

<sup>i</sup> Providers can consult with interventional radiology or vascular surgery colleagues to determine the appropriate use of mechanical embolectomy, suction embolectomy, and US-facilitated catheter-directed thrombolysis devices at their institutions.

<sup>j</sup> Decision to offer thrombolysis should be based on local availability/expertise, location of thrombus, and risk of bleeding. Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. See [Thrombolytic Agents \(VTE-H\)](#).

<sup>k</sup> [Contraindications to Thrombolysis and Indications for Thrombolysis \(VTE-I\)](#).

**Note: All recommendations are category 2A unless otherwise indicated.**



### THERAPEUTIC ANTICOAGULATION FOR VTE

#### General Guidelines

- Anticoagulation options recommended for management of VTE in patients with cancer include regimens involving only one agent (monotherapy) as well as regimens that use more than one type of agent (combination therapy). This section lists the recommended regimens, including dosing and duration, as well as a list of contraindications and warnings to help guide treatment selection.<sup>1</sup>
  - ▶ Duration of Anticoagulation as Recommended by Guideline:
    - ◊ Duration should be at least 3 months or as long as active cancer or cancer therapy.
    - ◊ For non-catheter-associated DVT or PE recommend indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist.
    - ◊ For symptomatic catheter-associated DVT, consider anticoagulation treatment for at least 3 months or as long as the catheter is in place.
    - ◊ 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 \(VTE-J\)](#).
    - ◊ Reconsider the role of anticoagulation therapy near the end of life. See [Elements for Consideration in Decision Not to Treat \(VTE-J\)](#).
- Select regimen based on these factors (not in order of importance): renal failure (CrCl <30 mL/min), hepatic disease (elevated transaminases or bilirubin, Child-Pugh B and C liver impairment, or cirrhosis), inpatient/outpatient status, U.S. Food and Drug Administration (FDA) approval, cost, patient preference, ease of administration, monitoring, bleeding risk assessment, and ability to reverse anticoagulation. See [Contraindications and Warnings \(VTE-D, 4 of 7\)](#).
- Baseline laboratory testing: CBC with platelet count, renal and hepatic function panel, aPTT, and PT/international normalized ratio (INR).
- Follow institutional standard operating procedures (SOPs) for dosing schedules. If there are no SOPs, then use the American College of Chest Physicians (ACCP) recommendations.<sup>2</sup>
- Following initiation of anticoagulant: hemoglobin, hematocrit, and platelet count at least every 2 to 3 days for the first 14 days while in the inpatient setting and every 2 weeks thereafter or as clinically indicated.
- DOACs, LMWH, and warfarin have all been used to treat patients with SPVT. Although published experience in the treatment of SPVT with DOACs is limited, results appear to be comparable to LMWH and warfarin. Therefore, we suggest that DOACs can be used for long-term treatment of SPVT in appropriate candidates in the recommended doses. In the absence of contraindications, NCCN suggests that DOACs, LMWH, and warfarin can be considered for treatment of SPVT. In patients with cancer, DOACs and LMWH are preferable to warfarin.

Note: All recommendations are category 2A unless otherwise indicated.

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# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### THERAPEUTIC ANTICOAGULATION FOR VTE (CONTINUED)<sup>§</sup>

#### DOACs (preferred for patients without gastric or gastroesophageal lesions)<sup>a</sup>

- Apixaban<sup>b,c</sup>
  - ▶ 10 mg PO every 12 hours for 7 days followed by 5 mg PO every 12 hours<sup>3-7,d</sup>
- Edoxaban<sup>b</sup>
  - ▶ Initial therapy with LMWH<sup>e</sup> or UFH<sup>f</sup> for at least 5 days followed by edoxaban 60 mg PO daily (or 30 mg PO daily in patients with Cockcroft-Gault estimated CrCl 30–50 mL/min or weight <60 kg or concomitant potent P-glycoprotein (P-gp) inhibitors)<sup>9,8,9</sup>
- Rivaroxaban
  - ▶ 15 mg PO every 12 hours for the first 21 days followed by 20 mg daily with food<sup>10-12</sup>

#### LMWH (preferred for patients with gastric or gastroesophageal lesions)

- Dalteparin<sup>b</sup>
  - ▶ 200 units/kg SC daily for 30 days, then switch to 150 units/kg once daily<sup>e,h,13,14</sup>
- Enoxaparin
  - ▶ 1 mg/kg SC every 12 hours (BMI <40 kg/m<sup>2</sup>) or 0.8 mg/kg SC every 12 hours (BMI ≥40 kg/m<sup>2</sup>) (can consider decreasing intensity to 1.5 mg/kg daily after first month)<sup>i,15-18</sup>

#### DOACs (if above regimens not appropriate or unavailable)<sup>a</sup>

- Dabigatran
  - ▶ Initial therapy with LMWH<sup>e</sup> or UFH<sup>f</sup> for at least 5 days followed by dabigatran 150 mg PO every 12 hours<sup>9,19</sup>

#### Fondaparinux<sup>20</sup>

- 5 mg SC daily (<50 kg)
- 7.5 mg SC daily (50–100 kg)
- 10 mg SC daily (>100 kg)

#### UFH (category 2B)

- IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs, followed by SC 250 units/kg every 12 hours (category 2B)
- SC 333 units/kg load, followed by 250 units/kg every 12 hours<sup>21</sup>

#### Warfarin<sup>j,22-24</sup>

- Start warfarin concurrently with LMWH, fondaparinux, or UFH (see dosing below)
- Warfarin 5 mg daily adjusted to INR 2–3 (2.5 mg daily initial dose for liver disease or use with interacting medications)
- The PT/INR can be prolonged by lupus inhibitors/anticoagulants, particularly point-of-care PT/INR.<sup>25</sup> See [Discussion](#) for further discussion of management.
  - ▶ LMWH + warfarin<sup>j</sup> options:
    - ◊ Dalteparin 200 units/kg SC daily or 100 units/kg SC every 12 hours
    - ◊ Enoxaparin 1 mg/kg SC every 12 hours
  - ▶ Fondaparinux + warfarin<sup>j,20</sup>
    - ◊ 5 mg SC daily (<50 kg)
    - ◊ 7.5 mg SC daily (50–100 kg)
    - ◊ 10 mg SC daily (>100 kg)
  - ▶ UFH + warfarin<sup>j</sup> options:
    - ◊ IV 80 units/kg bolus, followed by 18 units/kg/h adjusted to target aPTT of 2–2.5 X control or per hospital SOPs
    - ◊ SC 333 units/kg load, followed by 250 units/kg every 12 hours

<sup>§</sup> Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

Note: All recommendations are category 2A unless otherwise indicated.

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# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### FOOTNOTES

<sup>a</sup> Patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with DOACs.

<sup>b</sup> Category 1 for DVT/PE.

<sup>c</sup> Apixaban may be safer than edoxaban or rivaroxaban for patients with gastric or gastric esophageal lesions (category 2B).

<sup>d</sup> After 6 months of therapy, consider lower dose apixaban (2.5 mg every 12 hours) after assessment of patient's risk for recurrent VTE and bleeding (Mahé I, et al. N Engl J Med 2025;392:1363-1373).

<sup>e</sup> LMWH dosing options: Dalteparin 200 units/kg SC daily; Enoxaparin 1 mg/kg SC every 12 hours.

<sup>f</sup> UFH dosing options: IV 80 units/kg bolus, followed by 18 units/kg/h, adjusted to a target aPTT of 2–2.5x control or per hospital SOPs; SC 333 units/kg load, followed by 250 units/kg every 12 hours.

<sup>g</sup> Unlike warfarin, concurrent administration with parenteral anticoagulants is not recommended when transitioning to edoxaban or dabigatran. See prescribing information for protocols for transitioning between agents.

<sup>h</sup> Although each of the LMWH agents has been studied in randomized controlled trials in patients with cancer, 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.

<sup>i</sup> Long-term management with enoxaparin dosing of 1 mg/kg SC every 12 hours has not been tested in patients with cancer.

<sup>j</sup> 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 INR is  $\geq 2$ . 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 of 2–3, INR testing can be gradually decreased to a frequency of no less than once a month.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### THERAPEUTIC ANTICOAGULATION FOR VTE (CONTINUED)<sup>§</sup>

Agent(s)	Contraindications and Warnings		
<b>LMWH: Dalteparin and enoxaparin</b>	<ul style="list-style-type: none"> <li>• Use with caution in patients with renal dysfunction. Consider dose adjustments or alternative therapy for patients with severe renal dysfunction (CrCl &lt;30 mL/min).<sup>k</sup></li> <li>• Follow package insert for renal dysfunction dosing.</li> <li>• 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.</li> <li>• Absolute contraindication: recent/acute HIT</li> <li>• Relative contraindication: past history of HIT</li> <li>• Pork product allergy</li> </ul>		
<b>Fondaparinux</b>	<ul style="list-style-type: none"> <li>• Contraindicated in patients with CrCl &lt;30 mL/min</li> <li>• Use with caution in patients with moderate renal insufficiency (CrCl 30–50 mL/min), weight &lt;50 kg, or age &gt;75 y</li> </ul>		
<b>UFH</b>	<ul style="list-style-type: none"> <li>• Absolute contraindication: recent/acute HIT</li> <li>• Relative contraindication: past history of HIT</li> </ul>		
<b>Warfarin</b>	<p><b>Relative contraindications:</b></p> <ul style="list-style-type: none"> <li>• Concomitant inhibitors and inducers of CYP2C9, 1A2, or 3A4</li> </ul>		
<b>DOACs: Apixaban, dabigatran, edoxaban, and rivaroxaban</b>	<table border="1"> <tr> <td> <p><b>Contraindications:</b></p> <ul style="list-style-type: none"> <li>• Antiphospholipid syndrome (APS)<sup>l</sup></li> <li>• Pregnancy or breastfeeding</li> <li>• Stage IV/V chronic kidney disease: <ul style="list-style-type: none"> <li>▶ Apixaban<sup>m</sup>: CrCl &lt;30 mL/min<sup>4</sup></li> <li>▶ Dabigatran, edoxaban,<sup>26</sup> rivaroxaban<sup>12</sup>: CrCl &lt;30 mL/min</li> </ul> </li> <li>• Active/clinically significant liver disease: <ul style="list-style-type: none"> <li>▶ Apixaban<sup>6</sup>: Child-Pugh Class B or C or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) &gt;3x upper limit of normal (ULN); total bilirubin &gt;2x ULN</li> <li>▶ Rivaroxaban<sup>12</sup>: Child-Pugh class B or C or ALT/AST &gt;3x ULN</li> <li>▶ Dabigatran<sup>19,27–29</sup>: Child-Pugh class C or ALT/AST &gt;2x ULN or active/acute hepatitis or cirrhosis</li> <li>▶ Edoxaban<sup>8</sup>: Child-Pugh class B or C or AST/ALT &gt;3x ULN and bilirubin &gt;2x ULN, cirrhosis, or active hepatitis</li> <li>▶ Strong dual inhibitors/inducers of CYP3A4 and P-gp: see prescribing information for rivaroxaban and apixaban</li> </ul> </li> <li>• Inducers/inhibitors of P-gp: see prescribing information for dabigatran and edoxaban</li> </ul> </td><td> <p><b>Relative contraindications, use with caution:</b></p> <ul style="list-style-type: none"> <li>• DOACs have been associated with an increased risk of GI and possibly genitourinary tract bleeding, and should be used with caution in patients with genitourinary or GI tract lesions, pathology, or instrumentation.</li> <li>• Use with caution in patients with compromised renal or liver function.</li> <li>• For patients receiving nephrotoxic or hepatotoxic chemotherapy, consider monitoring patients more closely with laboratory testing.</li> <li>• Consider drug-drug interactions.</li> </ul> </td></tr> </table>	<p><b>Contraindications:</b></p> <ul style="list-style-type: none"> <li>• Antiphospholipid syndrome (APS)<sup>l</sup></li> <li>• Pregnancy or breastfeeding</li> <li>• Stage IV/V chronic kidney disease: <ul style="list-style-type: none"> <li>▶ Apixaban<sup>m</sup>: CrCl &lt;30 mL/min<sup>4</sup></li> <li>▶ Dabigatran, edoxaban,<sup>26</sup> rivaroxaban<sup>12</sup>: CrCl &lt;30 mL/min</li> </ul> </li> <li>• Active/clinically significant liver disease: <ul style="list-style-type: none"> <li>▶ Apixaban<sup>6</sup>: Child-Pugh Class B or C or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) &gt;3x upper limit of normal (ULN); total bilirubin &gt;2x ULN</li> <li>▶ Rivaroxaban<sup>12</sup>: Child-Pugh class B or C or ALT/AST &gt;3x ULN</li> <li>▶ Dabigatran<sup>19,27–29</sup>: Child-Pugh class C or ALT/AST &gt;2x ULN or active/acute hepatitis or cirrhosis</li> <li>▶ Edoxaban<sup>8</sup>: Child-Pugh class B or C or AST/ALT &gt;3x ULN and bilirubin &gt;2x ULN, cirrhosis, or active hepatitis</li> <li>▶ Strong dual inhibitors/inducers of CYP3A4 and P-gp: see prescribing information for rivaroxaban and apixaban</li> </ul> </li> <li>• Inducers/inhibitors of P-gp: see prescribing information for dabigatran and edoxaban</li> </ul>	<p><b>Relative contraindications, use with caution:</b></p> <ul style="list-style-type: none"> <li>• DOACs have been associated with an increased risk of GI and possibly genitourinary tract bleeding, and should be used with caution in patients with genitourinary or GI tract lesions, pathology, or instrumentation.</li> <li>• Use with caution in patients with compromised renal or liver function.</li> <li>• For patients receiving nephrotoxic or hepatotoxic chemotherapy, consider monitoring patients more closely with laboratory testing.</li> <li>• Consider drug-drug interactions.</li> </ul>
<p><b>Contraindications:</b></p> <ul style="list-style-type: none"> <li>• Antiphospholipid syndrome (APS)<sup>l</sup></li> <li>• Pregnancy or breastfeeding</li> <li>• Stage IV/V chronic kidney disease: <ul style="list-style-type: none"> <li>▶ Apixaban<sup>m</sup>: CrCl &lt;30 mL/min<sup>4</sup></li> <li>▶ Dabigatran, edoxaban,<sup>26</sup> rivaroxaban<sup>12</sup>: CrCl &lt;30 mL/min</li> </ul> </li> <li>• Active/clinically significant liver disease: <ul style="list-style-type: none"> <li>▶ Apixaban<sup>6</sup>: Child-Pugh Class B or C or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) &gt;3x upper limit of normal (ULN); total bilirubin &gt;2x ULN</li> <li>▶ Rivaroxaban<sup>12</sup>: Child-Pugh class B or C or ALT/AST &gt;3x ULN</li> <li>▶ Dabigatran<sup>19,27–29</sup>: Child-Pugh class C or ALT/AST &gt;2x ULN or active/acute hepatitis or cirrhosis</li> <li>▶ Edoxaban<sup>8</sup>: Child-Pugh class B or C or AST/ALT &gt;3x ULN and bilirubin &gt;2x ULN, cirrhosis, or active hepatitis</li> <li>▶ Strong dual inhibitors/inducers of CYP3A4 and P-gp: see prescribing information for rivaroxaban and apixaban</li> </ul> </li> <li>• Inducers/inhibitors of P-gp: see prescribing information for dabigatran and edoxaban</li> </ul>	<p><b>Relative contraindications, use with caution:</b></p> <ul style="list-style-type: none"> <li>• DOACs have been associated with an increased risk of GI and possibly genitourinary tract bleeding, and should be used with caution in patients with genitourinary or GI tract lesions, pathology, or instrumentation.</li> <li>• Use with caution in patients with compromised renal or liver function.</li> <li>• For patients receiving nephrotoxic or hepatotoxic chemotherapy, consider monitoring patients more closely with laboratory testing.</li> <li>• Consider drug-drug interactions.</li> </ul>		

<sup>§</sup> Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

<sup>k</sup> There are limited data on long-term use of LMWH in patients with CrCl <30 mL/min.

<sup>l</sup> Warfarin is the preferred anticoagulant for most patients with APS. This is particularly true in patients with triple-positive APS or lupus inhibitors/anticoagulants but it has also been seen in patients with in single-and double-positive disease. DOACs should be used with caution (Knight JS, et al. BMJ. 2023;380:e069717).

<sup>m</sup> Although stage IV chronic kidney disease is not listed as a contraindication in the FDA-approved label for apixaban, the NCCN Panel acknowledges that there are observational data to support safe apixaban dosing in these patients, especially those who are on hemodialysis.

**Note: All recommendations are category 2A unless otherwise indicated.**

[References on VTE-D 6 of 7](#)



### THERAPEUTIC ANTICOAGULATION FOR VTE (CONTINUED) DOACs: GI CONSIDERATIONS AND ALTERNATIVE ROUTES OF ADMINISTRATION§

#### DOACs and GI Tract Surgery Considerations

- DOACs are absorbed primarily in the stomach and proximal small bowel (with the exception of apixaban, which is also absorbed in the distal small bowel and proximal colon), so they may not be appropriate for patients who have had significant resections of these portions of the intestinal tract. The table below provides absorption guidance following GI surgical interventions based on available data.<sup>30-32</sup>
- Retrospective cohort studies of patients who had bariatric and cancer GI surgery support the conclusion that apixaban drug levels are more likely to remain in the expected peak on treatment range than rivaroxaban after gastric or proximal small bowel resections. Dabigatran drug levels were below the peak on therapy range. Limited information is available for edoxaban but in the few patients studied, drug levels were in the expected peak on treatment range.<sup>33-36</sup>
- Although uncertainty remains about the association of drug levels and clinical outcomes, we recommend considering drug levels in patients taking DOACs post-GI tract surgery.

#### Enteral Feeding Tube Administration of DOACs

- Apixaban: For nasogastric/gastric feeding tube administration, crushed tablets may be suspended in 60 mL of water or D5W followed by immediate delivery. Crushed tablets are stable in water and D5W for up to 4 hours. Bioavailability is reduced if administered distal to the stomach.<sup>32</sup>
- Rivaroxaban: For nasogastric/gastric feeding tube administration, crushed tablets may be suspended in 50 mL of water and administered within 4 hours of preparation. Follow administration of the 15 mg and 20 mg tablets immediately with enteral feeding (2.5 mg and 10 mg tablets may be administered without regard to food). Avoid administration distal to the stomach, which can result in reduced absorption. A commercially prepared oral suspension formulation with an accompanying measuring syringe is also available for pediatric patients.<sup>32</sup>
- Edoxaban: Crushed tablets may be suspended in 2 to 3 ounces of water and immediately administered through a gastric tube.<sup>37</sup>
- Dabigatran: Should not be administered through an enteral feeding tube.<sup>32</sup>

Surgical Procedure	Anticoagulant Systemic Absorption			
	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Total or partial gastrectomy	Possibly reduced <sup>31,32</sup> or not impacted <sup>38</sup>	Possibly reduced <sup>31,32</sup>	Possibly reduced <sup>31,44</sup>	Possibly reduced <sup>46</sup> or not impacted <sup>45,46</sup>
Roux-en-Y gastric bypass (RYGB)	Possibly reduced <sup>31,32</sup> or not impacted <sup>39</sup>	Possibly reduced <sup>31,32,41,42</sup>	Possibly reduced <sup>31</sup>	Possibly reduced <sup>31,32</sup> or not impacted <sup>45,46</sup>
Distal resection and short bowel syndrome	Possibly reduced <sup>31,40</sup>	Possibly reduced <sup>31,43</sup>	Unlikely to be affected <sup>31</sup>	Unlikely to be affected <sup>31,47</sup>
Colectomy	Possibly reduced <sup>31,40</sup>	Unlikely to be affected <sup>31</sup>	Unlikely to be affected <sup>31</sup>	Unlikely to be affected <sup>31</sup>

§ Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

Note: All recommendations are category 2A unless otherwise indicated.

[References on VTE-D 6 of 7](#)

### THERAPEUTIC ANTICOAGULATION FOR VTE REFERENCES

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**Note: All recommendations are category 2A unless otherwise indicated.**





# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### THERAPEUTIC ANTICOAGULATION FOR VTE REFERENCES

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**Note: All recommendations are category 2A unless otherwise indicated.**





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## Cancer-Associated Venous Thromboembolic Disease

### CONTRAINDICATIONS TO THERAPEUTIC ANTICOAGULATION<sup>a</sup>

- **Absolute contraindications**

- ▶ **Active bleeding (major)<sup>b</sup>**
- ▶ **Indwelling neuraxial catheters**
- ▶ **Neuraxial anesthesia/lumbar puncture<sup>c,d</sup>**
- ▶ **Interventional spine and pain procedures<sup>1</sup>**

- **Relative contraindications**

- ▶ **Chronic, clinically significant measurable bleeding >48 hours**
- ▶ **Thrombocytopenia (platelet count <30,000 to 50,000/μL or clinical judgment)<sup>e</sup>**
- ▶ **Underlying hemorrhagic coagulopathy (eg, abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (eg, hemophilia, von Willebrand disease)**
- ▶ **Severe platelet dysfunction**
- ▶ **Recent major operation at high risk for bleeding**
- ▶ **High risk for falls (head trauma)**
- ▶ **Primary and metastatic brain tumors<sup>f</sup>**
- ▶ **Long-term antiplatelet therapy<sup>g</sup>**

<sup>1</sup> Narouze S, Benzon HT, Provenzano D, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med* 2015;40:182-212.

<sup>a</sup> For agent-specific contraindications, see [VTE-D](#).

<sup>b</sup> Active bleeding with >2 units red blood cells (RBCs) transfused, decrease in hemoglobin by ≥2 g/dL, or intracranial or intraspinal bleeding.

<sup>c</sup> Refer to institutional-specific anesthesia practice guidelines, if available. Twice-daily prophylactic dose UFH (5000 units every 12 h) and once-daily LMWH (eg, enoxaparin 40 mg once daily) may be used with neuraxial anesthesia. Twice-daily prophylactic dose LMWH (eg, enoxaparin 30 mg every 12 h), prophylactic dose fondaparinux (2.5 mg daily), and therapeutic dose anticoagulation should be used with extreme caution with neuraxial anesthesia. The safety of thrice-daily prophylactic dose UFH in conjunction with neuraxial anesthesia has not been established (Horlocker TT, Wedel DJ, Rowlingson JC, et al. *Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines [Third Edition]*. *Reg Anesth Pain Med* 2010;35:64-101).

<sup>d</sup> Timing of LMWH: For LMWH, placement or removal of a neuraxial catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of DVT. Longer delays (24 h) are appropriate to consider for patients receiving therapeutic doses of LMWH. A post-procedure dose of LMWH should usually be given no sooner than 4 hours after catheter removal (FDA Drug Safety Communications. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on LMWH. November 6, 2013: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM373735.pdf>). In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.

<sup>e</sup> [Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia \(VTE-F\)](#).

<sup>f</sup> In general, brain metastases are a relative contraindication to anticoagulation except in cases where more caution is warranted due to the location of the metastases, tumor type (eg, thyroid, melanoma, renal, choriocarcinoma), or presence of other comorbidities.

<sup>g</sup> For patients on long-term antiplatelet therapy, reassess the need for antiplatelet therapy and discontinue/reduce dose of antiplatelet treatment if possible.

**Note: All recommendations are category 2A unless otherwise indicated.**



### MANAGEMENT OF ANTICOAGULATION FOR VTE IN PATIENTS WITH CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

- Thrombocytopenia is a common occurrence in patients with cancer who are receiving therapeutic anticoagulation for cancer-associated thrombosis. Generally, anticoagulation is considered safe with platelet counts  $\geq 50,000/\mu\text{L}$ . The risk of bleeding is thought to increase as platelet counts decline below this threshold. Traditionally, physicians have transfused platelet concentrations to maintain platelet counts above  $50,000/\mu\text{L}$  in patients with thrombocytopenia on therapeutic anticoagulation, but this is not always feasible depending upon the duration and severity of thrombocytopenia and availability of blood products.
- When managing cancer-associated thrombosis with thrombocytopenia the provider should consider:
  - The patient's risk for recurrent thromboembolism, and
  - The patient's risk of bleeding including the anticipated depth and duration of thrombocytopenia
- For patients at high risk of recurrent thromboembolism (includes recent proximal DVT or PE [within 1 month of anticoagulation treatment], recurrent thromboembolism) management options include:
  - Continuation of therapeutic dose anticoagulation while maintaining platelet count  $\geq 50,000/\mu\text{L}$  with platelet transfusions
  - Placement of a retrievable IVC filter and discontinuation of anticoagulation until platelet recovery
- For patients at lower risk for recurrent thromboembolism (includes DVT/PE occurring after more than 1 month of anticoagulation treatment, central venous catheter-associated DVT, upper extremity DVT, acute distal DVT) management options include:
  - Use of lower dose anticoagulation as outlined below in the table
  - Removal of central venous catheter in patients with central venous catheter-associated DVT
  - Monitoring of distal DVT with serial US surveillance while patient is off anticoagulation (if clot extends to proximal venous system, then manage as acute high risk)

#### Enoxaparin Dose Modification in the Setting of Thrombocytopenia

Platelet Count	Dose Adjustment	Suggested Dose of Enoxaparin	Alternative Once-Daily Dosing Regimen
$>50,000/\mu\text{L}$	Full-dose enoxaparin	1 mg/kg twice daily	1.5 mg/kg daily
25,000–50,000/ $\mu\text{L}$	Half-dose enoxaparin	0.5 mg/kg twice daily	—
$<25,000/\mu\text{L}$	Temporarily hold enoxaparin		

- Note: NCCN currently does not recommend use of DOACs below a platelet count of  $50,000/\mu\text{L}$  as there is limited published experience using DOACs in this situation.

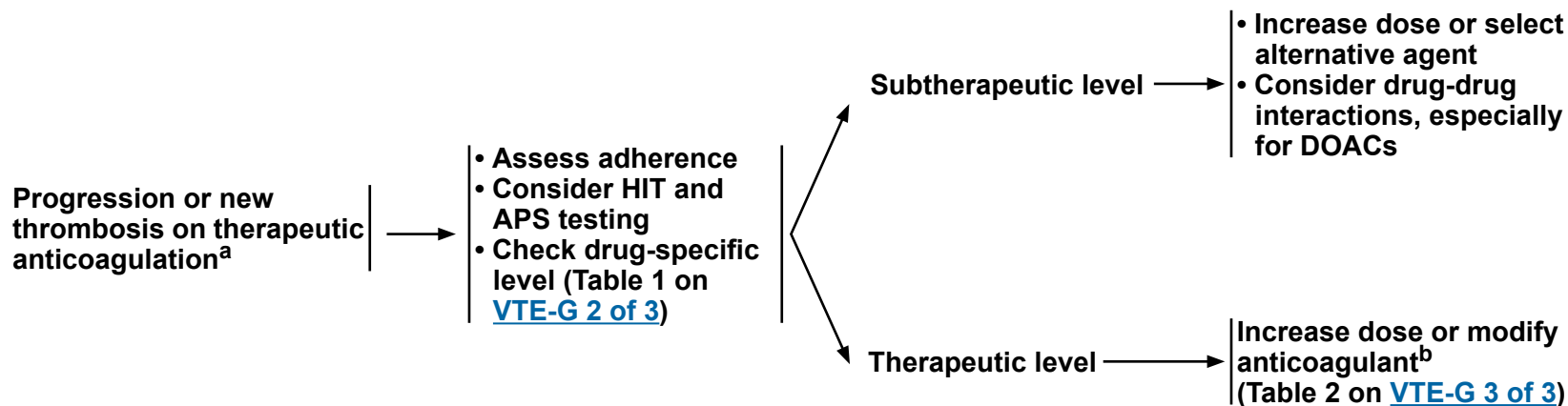
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## Cancer-Associated Venous Thromboembolic Disease

### PROGRESSION OR NEW THROMBOSIS ON THERAPEUTIC ANTICOAGULATION



<sup>a</sup> Progression or new thrombosis on therapeutic anticoagulation is defined as an extension of DVT or new DVT or PE while on therapeutic levels of recommended anticoagulation therapy. An early embolism event might not indicate progression or new thrombosis on therapeutic anticoagulation. See [Therapeutic Anticoagulation for VTE \(VTE-D\)](#).

<sup>b</sup> Conditions associated with venous stasis such as vascular compression by tumors or lymphatic masses or stasis associated with IVC filters can cause recurrent thrombosis despite therapeutic anticoagulation. Uncontrolled myeloproliferative neoplasms or paroxysmal nocturnal hemoglobinuria can also be responsible for this phenomenon. Relief of vascular stasis or treatment of MPN/PNH can reduce the risk of recurrence.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### PROGRESSION OR NEW THROMBOSIS ON THERAPEUTIC ANTICOAGULATION

Table 1: Therapeutic Range of Anticoagulants

Anticoagulation Agent	Drug-level	Adjustment
UFH	UFH anti-Xa or aPTT	<ul style="list-style-type: none"><li>• Calibrated to UFH</li><li>• In patients with lupus inhibitor/anticoagulant or prolonged baseline aPTT, UFH anti-Xa level should be used for dose titration</li></ul>
LMWH	LMWH anti-Xa	<ul style="list-style-type: none"><li>• Calibrated to LMWH</li></ul>
Fondaparinux	Fondaparinux anti-Xa	<ul style="list-style-type: none"><li>• Calibrated to fondaparinux</li></ul>
Warfarin	INR	<ul style="list-style-type: none"><li>• Goal 2–3 if baseline INR is normal</li><li>• In patients with prolonged baseline PT/INR or lupus inhibitor/anticoagulant, target INR range should be confirmed with factor X activity or chromogenic factor X activity, respectively</li></ul>
Apixaban	Apixaban anti-Xa	<ul style="list-style-type: none"><li>• No established "therapeutic range." Peak/trough levels observed in the clinical trials for apixaban may serve as point of reference but should not be used to make dose adjustments/titrations.</li></ul>
Dabigatran	Ecarin clotting time or diluted thrombin time (dTT)	<ul style="list-style-type: none"><li>• No established "therapeutic range." Peak/trough levels observed in the clinical trials for dabigatran may serve as point of reference but should not be used to make dose adjustments/titrations.</li></ul>
Edoxaban	Edoxaban anti-Xa	<ul style="list-style-type: none"><li>• No established "therapeutic range." Peak/trough levels observed in the clinical trials for edoxaban may serve as point of reference but should not be used to make dose adjustments/titrations.</li></ul>
Rivaroxaban	Rivaroxaban anti-Xa	<ul style="list-style-type: none"><li>• No established "therapeutic range." Peak/trough levels observed in the clinical trials for rivaroxaban may serve as point of reference but should not be used to make dose adjustments/titrations.</li></ul>

Note: All recommendations are category 2A unless otherwise indicated.



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### PROGRESSION OR NEW THROMBOSIS ON THERAPEUTIC ANTICOAGULATION

**Table 2: Alternative Anticoagulant Options in Case of Progression or New Thrombosis on Therapeutic Anticoagulation**

Failed Anticoagulant	Alternative Anticoagulant(s) <sup>c</sup>
UFH	<ul style="list-style-type: none"> <li>• Confirm therapeutic aPTT with UFH anti-Xa level</li> <li>• Switch to alternative anticoagulant (DOACs [apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B], LMWH, warfarin, fondaparinux)</li> <li>• Increase dose of UFH. Use UFH anti-Xa levels to titrate UFH (in the event of recurrence in setting of subtherapeutic anti-Xa levels).</li> </ul>
LMWH	<ul style="list-style-type: none"> <li>• Change to every-12-hour dosing</li> <li>• Switch to DOAC (apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B), UFH, or fondaparinux</li> <li>• Increase dose of LMWH<sup>d,e</sup></li> </ul>
Fondaparinux	• Switch to LMWH, DOAC (apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B), UFH
Warfarin	<ul style="list-style-type: none"> <li>• If factor X activity or chromogenic factor X activity is low despite therapeutic PT/INR, increase dose of warfarin and titrate to PT/INR range based upon therapeutic factor X or chromogenic factor X activity</li> <li>• Switch to LMWH, DOAC (apixaban, dabigatran, edoxaban, rivaroxaban; all category 2B), UFH, fondaparinux</li> </ul>
Apixaban	• Switch to LMWH, UFH, fondaparinux
Dabigatran	• Switch to LMWH, UFH, fondaparinux
Edoxaban	• Switch to LMWH, UFH, fondaparinux
Rivaroxaban <sup>f</sup>	• Switch to LMWH, UFH, fondaparinux

<sup>c</sup> As renal function allows.

<sup>d</sup> LMWH (anti-Xa) levels may be considered in patients with body weight extremes, renal impairment, or for whom adherence is a concern. Obtain LMWH anti-Xa level 3–5 hours after the third dose to assess dosing. Adjustments may be needed to the dose according to anti-Xa levels, with a recommended peak of 0.6–1.0 units/mL (1 mg/kg twice-daily dosing) or peak of 1–2 units/mL (1.5 mg/kg once-daily dosing).

<sup>e</sup> Although data are limited, doses are generally increased to 120%–125% of full dose for LMWH and fondaparinux (Ihaddadene R, Le Gal G, Delluc A, Carrier M. Dose escalation of low molecular weight heparin in patients with recurrent cancer-associated thrombosis. *Thromb Res* 2014;134:93-95; Carrier M, Le Gal G, Cho R, et al. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. *J Thromb Haemost* 2009;7:760-765).

<sup>f</sup> Ensure taking with largest meal of the day to promote absorption.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### THROMBOLYTIC AGENTS

- **DVT<sup>a,b</sup>:**
  - ▶ **Pharmacomechanical devices<sup>b,1</sup>**
    - ◊ **Alteplase 10 mg to 25 mg per session**
  - ▶ **Infusion catheters<sup>b,1</sup>**
    - ◊ **Alteplase 0.5 mg to 1 mg per hour for 12–24 hours**
    - ◊ **Reteplase 0.5 unit to 1 unit per hour for 12–24 hours**
- **SPVT**
  - ▶ **Thrombolysis with catheter-directed therapies is limited to case reports and small studies. Follow local institutional protocols.**

- **PE**
  - ▶ **Systemic thrombolysis**
    - ◊ **Alteplase 100 mg IV over 2 hours<sup>c</sup>**
    - ◊ **Alteplase 50 mg as a 10 mg bolus followed by 20 mg per hour for 2 hours<sup>c,2</sup>**
    - ◊ **Reteplase 10 unit IV bolus followed 30 minutes later by a second 10 unit IV bolus injection, both doses administered over 2 minutes<sup>3</sup>**
    - ◊ **Tenecteplase (category 2B)<sup>4</sup>**

Weight	Tenecteplase Dose
<60 kg	30 mg
≥60 to <70 kg	35 mg
≥70 to <80 kg	40 mg
≥80 to <90 kg	45 mg
≥90 kg	50 mg

- ▶ **US-assisted, catheter-directed thrombolysis<sup>5</sup>**
  - ◊ **Alteplase 1 mg per hour per lung for 12–24 hours<sup>d</sup>**

<sup>1</sup> Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med* 2017;377:2240-2252.

<sup>2</sup> Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" trial). *Am J Cardiol* 2013;111:273-277.

<sup>3</sup> Tebbe U, Graf A, Kamke W, et al. Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. *Am Heart J* 1999;138:39-44; Liu Z, Wang J. The use of reteplase in patients with pulmonary embolism reteplase after haemodynamic changes. *Heart* 2012;98(Suppl 2):E281-282.

<sup>4</sup> Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370:1402-1411.

<sup>5</sup> Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE Trial. *JACC Cardiovasc Interv* 2018;11:1401-1410.

<sup>a</sup> A post-procedural imaging study is recommended to confirm the results of thrombolysis.

<sup>b</sup> Different FDA-approved catheters and devices exist to deliver thrombolytic agents into the thrombus in conjunction with mechanical thrombectomy. No single catheter or device has been proven to be superior to another. The extent of thrombus may be an important factor in device and agent selection as well as the likelihood of success.

<sup>c</sup> Alteplase 50 mg may be appropriate for patients aged >75 years, with recent surgery (within 1 month), or with high risk of bleed.

<sup>d</sup> US-assisted, catheter-directed thrombolysis has been used for patients with PE with ≥50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥25 mmHg) or echocardiographic evaluation. Alteplase is administered at a rate of 1 mg/h per drug delivery catheter (2 mg/h for bilateral PE). Alteplase is infused for 24 hours with one catheter and 12 hours for two catheters.

**Note: All recommendations are category 2A unless otherwise indicated.**





### CONTRAINDICATIONS TO THROMBOLYSIS AND INDICATIONS FOR THROMBOLYSIS

#### Contraindications to Thrombolysis<sup>a,b</sup>

- **Absolute**
  - History of hemorrhagic stroke or intracranial hemorrhage
  - Intracranial tumor
  - Ischemic stroke in previous 3 months
  - History of major trauma, surgery, or head injury in previous 3 weeks
  - Active bleeding
  - Bleeding diathesis
- **Relative**
  - Age >75 years
  - Pregnancy or first postpartum week
  - Non-compressible puncture sites
  - Traumatic resuscitation
  - Platelet count <100,000/μL
  - Refractory hypertension  
(systolic pressure >180 mmHg; diastolic blood pressure >100 mmHg)
  - Advanced liver disease
  - Infective endocarditis
  - Recent GI bleed (last 3 months)
  - Life expectancy ≤1 year

#### Indications for Thrombolysis

- Limb-threatening/life-threatening acute proximal DVT
- Severely symptomatic iliofemoral thrombosis (select patients)
- Massive/life-threatening PE
- Intestinal SPVT with high risk of ischemia

<sup>a</sup> Reproduced and adapted with permission from Kearon C, Akl E, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e419S-e494S.

<sup>b</sup> The risks and benefits of thrombolysis should be assessed on a case-by-case basis by the clinician caring for the patient. Use of a thrombolytic agent may be considered in pregnant and lactating individuals with life-threatening thrombosis. Studies examining the safety of thrombolytic therapy during pregnancy or lactation are not available, but thrombolytic agents are unlikely to cross the placenta or transfer to breast milk due to their large molecular weight.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### ELEMENTS FOR CONSIDERATION IN DECISION NOT TO TREAT

- Patient non-acceptance
- No therapeutic advantage
  - ▶ Limited survival
  - ▶ High bleeding risk
  - ▶ No planned oncologic intervention
- No palliative benefit (eg, alleviate dyspnea, prevent leg swelling)
- Unreasonable burden of anticoagulation treatment
  - ▶ Painful injections
  - ▶ Frequent monitoring with phlebotomy
- End-of-life/comfort care

**Note: All recommendations are category 2A unless otherwise indicated.**



### REVERSAL OF ANTICOAGULATION

- In the event of life-threatening bleeding or the need for urgent/emergent invasive procedures, anticoagulant effect must be reversed promptly.
- All anticoagulation reversal protocols are associated with a risk of thromboembolism.
- It is recommended that institutions have treatment pathways or guidelines for the reversal of anticoagulation, which might make use of the agents listed below:
  - ▶ 4-factor prothrombin complex concentrate (PCC)
  - ▶ Andexanet alfa
  - ▶ Idarucizumab
  - ▶ Oral charcoal
  - ▶ Protamine
  - ▶ Recombinant human coagulation Factor VIIa (rhFVIIa)
  - ▶ Activated prothrombin complex concentrates (aPCC) (anti-inhibitor coagulant complex, vapor heated)
  - ▶ Vitamin K<sub>1</sub> oral (phytonadione) and IV solution

- The reversal guidelines for different anticoagulants are displayed in the following tables:

Heparin	Reversal of Anticoagulation	Precautions/Additional Considerations
• UFH (Half-life 1 hour)	<ul style="list-style-type: none"><li>• Protamine 1 mg/100 units of UFH (taking into account UFH ~1-hour half-life) by slow IV infusion (no faster than 5 mg per min)</li><li>• Follow aPTT or anti-Xa levels in accordance with institutional SOP closely</li><li>• Maximum dose: 50 mg</li><li>Examples:<ul style="list-style-type: none"><li>▶ Bleeding immediately after 5000 units bolus and patient is given 50 mg of protamine</li><li>▶ Patient on 1250 units per hour bleeds and is given 24 mg of protamine to reverse the UFH remaining from the last 4 hours of the infusion</li></ul></li></ul>	<ul style="list-style-type: none"><li>• Protamine can cause anaphylaxis if administered too rapidly. Protamine can also cause significant hypotension, bradycardia, and pulmonary hypertension, so monitor blood pressure, heart rate, and oxygenation closely during administration.</li><li>• Patients with fish allergies, previous exposure to protamine (eg, NPH insulin), or individuals who have had a vasectomy or individuals assigned male at birth who are infertile are at increased risk.</li><li>• Excessive protamine (protamine: heparin ratios &gt;1.3:1 mg/U) are associated with platelet dysfunction and decreased thrombin activity, resulting in bleeding.</li></ul>
• LMWH (Half-life 4.5–7 hours)	<ul style="list-style-type: none"><li>• Protamine 1 mg/mg of enoxaparin or 1 mg/100 units of dalteparin within 8 hours of dose</li><li>• Protamine 0.5 mg/mg of enoxaparin or 0.5 mg/100 units of dalteparin if dose administered &gt;8 hours prior</li><li>• If &gt;12 hours since dose, consider clinical scenario (eg, LMWH dose, renal function, bleeding severity) when deciding whether protamine is indicated</li><li>• Administer protamine by slow IV infusion (no faster than 5 mg per min)</li><li>• Maximum dose: 50 mg</li></ul>	<ul style="list-style-type: none"><li>• Protamine reverses a variable amount of LMWH anti-Xa activity.</li><li>• In the event of ongoing bleeding and persistent drug levels, consider a second dose of protamine.</li></ul>

Note: All recommendations are category 2A unless otherwise indicated.

[References on VTE-K 8 of 8](#)



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### REVERSAL OF ANTICOAGULATION

DTI	Reversal of Anticoagulation	Precautions/Additional Considerations
<ul style="list-style-type: none"><li>• Bivalirudin<sup>a</sup> (half-life 25 minutes with normal renal function)</li></ul>	<ul style="list-style-type: none"><li>• Discontinue drug.</li><li>• No specific antidote exists, but beneficial effects have been ascribed to the following:<ul style="list-style-type: none"><li>▶ Hemofiltration and hemodialysis are effective in removal of bivalirudin.</li><li>▶ Animal models and ex-vivo experiments suggest aPCCs (50–100 units/kg IV at 2 units per kg body weight per minute) or rhFVIIa (90 mcg/kg IV over 2–5 minutes) may be effective.</li><li>▶ Monitor reversal with aPTT.</li></ul></li></ul>	<ul style="list-style-type: none"><li>• Limited data exist to support all reversal strategies.</li></ul>
<ul style="list-style-type: none"><li>• Argatroban<sup>b</sup> (half-life 39–51 minutes)</li></ul>	<ul style="list-style-type: none"><li>• Discontinue drug.</li><li>• No specific antidote exists, but beneficial effects have been ascribed to the following:<ul style="list-style-type: none"><li>▶ Animal models and case reports suggest PCCs and aPCCs (50–100 units/kg IV) may be effective.</li><li>▶ Ex-vivo studies suggest rhFVIIa (90 mcg/kg IV) also may be effective.</li><li>▶ Monitor reversal with aPTT.</li></ul></li></ul>	

<sup>a</sup> Limited information is available on the clinical efficacy of all these proposed reversal strategies. For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of rhFVIIa as the first-line agent. Hemofiltration or hemodiafiltration can accelerate the clearance of bivalirudin.

<sup>b</sup> Limited information is available on the clinical efficacy of all these proposed reversal strategies. For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of aPCC or rhFVIIa as the first-line agent.

**Note: All recommendations are category 2A unless otherwise indicated.**

[References on VTE-K 8 of 8](#)



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### REVERSAL OF ANTICOAGULATION

DTI	Reversal of Anticoagulation	Precautions/Additional Considerations
<ul style="list-style-type: none"><li>• Dabigatran<sup>b</sup> (half-life 12–17 hours)</li></ul>	<ul style="list-style-type: none"><li>• Discontinue drug.</li><li>• Administer idarucizumab, 2.5 g in 2 consecutive boluses.</li><li>• Oral charcoal if dose within 2 hours of ingestion<ul style="list-style-type: none"><li>▶ Standard initial adult dose 50–100 g followed by doses every 1, 2, or 4 hours equivalent to 12.5 g/h</li></ul></li><li>• For special situations with slow or incomplete clearance (eg, renal dysfunction or failure), consider adding to idarucizumab:<ul style="list-style-type: none"><li>▶ Hemodialysis</li><li>▶ Hemodialysis with a charcoal filter</li></ul></li><li>• Monitor reversal with aPTT or dTT or Hemoclot thrombin inhibitor test to ensure complete reversal.</li></ul>	<ul style="list-style-type: none"><li>• Limited data exist to support all reversal strategies.</li><li>• In patients with renal failure/severe renal insufficiency, dialysis may be helpful in addition to idarucizumab.</li><li>• Idarucizumab is associated with thromboembolism within 30 days.</li></ul>

Factor Xa Inhibitor	Reversal of Anticoagulation	Precautions/Additional Considerations
<ul style="list-style-type: none"><li>• Fondaparinux (half-life 17–21 hours)</li></ul>	<ul style="list-style-type: none"><li>• Discontinue drug. No specific antidote exists; however, limited data suggest rhFVIIa (90 mcg/kg IV) may be beneficial.</li></ul>	<ul style="list-style-type: none"><li>• rhFVIIa has been associated with thromboembolic events.</li></ul>

<sup>b</sup> Limited information is available on the clinical efficacy of all these proposed reversal strategies. For life-threatening bleeding, the NCCN Guidelines Panel currently favors use of aPCC or rhFVIIa as the first-line agent.

**Note: All recommendations are category 2A unless otherwise indicated.**

[References on VTE-K 8 of 8](#)



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### REVERSAL OF ANTICOAGULATION

Direct Factor Xa Inhibitor	Reversal of Anticoagulation	Precautions/Additional Considerations
<ul style="list-style-type: none"><li>• Rivaroxaban (Half-life 5–9 hours for patients 20–45 years; 11–13 hours for patients 60–76 years)</li></ul> OR <ul style="list-style-type: none"><li>• Apixaban (Half-life 12 hours)</li></ul> OR <ul style="list-style-type: none"><li>• Edoxaban (Half-life 10–14 hours)</li></ul>	<p>Discontinue drug. Beneficial effects have been ascribed to the following:</p> <ul style="list-style-type: none"><li>• Consider oral charcoal if dose within 2 hours of ingestion and repeat within 6 hours<ul style="list-style-type: none"><li>▶ Standard initial adult dose 50–100 g followed by doses every 1, 2, or 4 hours equivalent to 12.5 g/h</li></ul></li><li>• Administer:<ul style="list-style-type: none"><li>▶ Andexanet alfa (consider for patients with intracranial hemorrhage)</li><li>▶ PCC<ul style="list-style-type: none"><li>◇ 4-factor PCC 25–50 units per kg (based on units of Factor IX per kg of actual body weight) or fixed dose of 2000 units</li><li>◇ If 4-factor PCC is unavailable or patient is allergic to heparin and/or has a history of HIT in the last 12 months, then administer 3-factor PCC 50 units/kg (based on units of Factor IX per kg of actual body weight)</li></ul></li></ul></li></ul>	<ul style="list-style-type: none"><li>• See andexanet alfa dosing and administration tables (<a href="#">VTE-K 7 of 8</a>).</li><li>• Andexanet alfa is associated with thromboembolism within 30 days of administration.</li><li>• aPCC and 4-factor PCC have been associated with a risk of thromboembolism when used for reversal of direct factor Xa inhibitors.</li><li>• Drug-specific anti-Xa assays should not be used to assess reversal of direct factor Xa inhibitors after administration of andexanet alfa, as they are not interpretable.</li></ul>

Note: All recommendations are category 2A unless otherwise indicated.

[References on VTE-K 8 of 8](#)





# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### REVERSAL OF ANTICOAGULATION

Warfarin (effective half-life 20–60 hours)	Reversal of Anticoagulation	Precautions/Additional Considerations
<ul style="list-style-type: none"><li>• INR 4.5–10, no bleeding</li></ul>	<ul style="list-style-type: none"><li>• Hold warfarin dose.</li><li>• Look for drug or dietary interactions and eliminate them if possible.</li><li>• Look for evidence of acute hepatic dysfunction/injury.</li><li>• Follow INR closely<sup>c</sup> (at least daily as an inpatient, every 1–2 days as outpatient).</li><li>• When INR approaches therapeutic range (INR &lt;4) restart warfarin at reduced dose (10%–20% dose reduction) if causal factor not present or cannot be eliminated.</li><li>• Recheck INR within 4–7 days.</li><li>• Adjust warfarin dose based on weekly INR until stable.</li></ul>	<ul style="list-style-type: none"><li>• N/A</li></ul>
<ul style="list-style-type: none"><li>• INR &gt;10, no bleeding</li></ul>	<ul style="list-style-type: none"><li>• Hold warfarin dose.</li><li>• Consider small dose of oral vitamin K<sub>1</sub> 1–2.5 mg in patients at high risk of bleeding (may repeat dose in 24 hours if INR remains elevated).</li><li>• Look for drug or dietary interactions and eliminate them if possible.</li><li>• Look for evidence of acute hepatic dysfunction/injury.</li><li>• Follow INR closely<sup>c</sup> (at least daily as an inpatient, every 1–2 days as outpatient).</li><li>• When INR approaches therapeutic range (INR &lt;4) restart warfarin at reduced dose (at least 20% dose reduction) if causal factor not present or cannot be eliminated.</li><li>• Recheck INR within 4–7 days.</li><li>• Adjust warfarin dose based on weekly INR until stable.</li></ul>	<ul style="list-style-type: none"><li>• Avoid vitamin K<sub>1</sub> SC administration due to erratic absorption, and delayed onset compared with oral administration.</li><li>• Vitamin K<sub>1</sub> IV administration can be used for more rapid absorption than tablets.</li></ul>

<sup>c</sup> The impact of warfarin dose changes can take at least 5 to 7 days to be fully manifested in the INR.

**Note:** All recommendations are category 2A unless otherwise indicated.

[References on VTE-K 8 of 8](#)



### REVERSAL OF ANTICOAGULATION

Warfarin (effective half-life 20–60 hours)	Reversal of Anticoagulation	Precautions/Additional Considerations
<ul style="list-style-type: none"><li>• Management of urgent surgery (within 24–48 hours)</li></ul>	<p><b>Within 24 hours:</b></p> <ul style="list-style-type: none"><li>• Hold warfarin dose</li><li>• Administer vitamin K<sub>1</sub> 1–2.5 mg IV slowly (no faster than 1 mg/min)</li><li>• Repeat INR preoperative to determine need for supplemental PCC</li></ul> <p><b>Within 48 hours:</b></p> <ul style="list-style-type: none"><li>• Hold warfarin dose</li><li>• Administer vitamin K<sub>1</sub> 2.5 mg orally</li><li>• Repeat INR at 24 and 48 hours to assess need for supplemental vitamin K<sub>1</sub> or PCC</li></ul>	<ul style="list-style-type: none"><li>• Infection due to pathogen transmission (all plasma-derived agents; greater risk with fresh frozen plasma [FFP] compared with solvent/detergent-treated products [3- or 4-factor PCC, aPCC])</li><li>• Immune reactions, including allergic/anaphylactic, alloimmunization (vitamin K<sub>1</sub> and all plasma-derived agents; greater risk with FFP compared with solvent/detergent-treated products [3- or 4-factor PCC, aPCC])</li></ul>
<ul style="list-style-type: none"><li>• Life-threatening bleeding</li></ul>	<ul style="list-style-type: none"><li>• Hold warfarin dose</li><li>• Administer vitamin K<sub>1</sub> 10 mg IV slowly (no faster than 1 mg/min)</li><li>• Administer 4-factor PCC<ul style="list-style-type: none"><li>▶ 4-factor PCC dosing (based on units of Factor IX per kg of actual body weight)<ul style="list-style-type: none"><li>◇ INR 2 to &lt;4: 25 units/kg (maximum 2500 units)</li><li>◇ INR 4–6: 35 units/kg (maximum 3500 units)</li><li>◇ INR &gt;6: 50 units/kg (maximum 5000 units)</li></ul></li><li>▶ If 4-factor PCC unavailable or patient is allergic to heparin and/or a history of HIT in the last 12 months:<ul style="list-style-type: none"><li>◇ INR &lt;4: 3-factor PCC 25 units/kg + FFP 2–3 units</li><li>◇ INR &gt;4: 3-factor PCC 50 units/kg + FFP 2–3 units</li></ul></li><li>▶ FFP 15 mL/kg (consider if PCC unavailable)</li><li>▶ rhFVIIa 25 mcg/kg (consider if PCC is unavailable or bleeding is unresponsive to PCC)</li></ul></li><li>• Monitor INR closely</li><li>• Consider repeating administration depending on clinical or laboratory parameters</li></ul>	<ul style="list-style-type: none"><li>• Three hours or longer may be required for phytonadione to halt or slow active bleeding. Rapid administration of IV vitamin K<sub>1</sub> is associated with a higher risk of anaphylaxis (risk ~1 in 3000 doses).</li><li>• Monitor vital signs closely.</li><li>• Administer 4-factor PCC (contains heparin) IV push at a rate not exceeding 5 mL/min.</li><li>• PCCs are associated with a risk of thromboembolism within 30 days of administration.</li><li>• Administer 3-factor PCC IV push at a rate not exceeding 10 mL/min.</li><li>• FFP is associated with thromboembolism within 30 days of administration.</li><li>• Administer rhFVIIa IV push over 2–5 minutes.</li><li>• rhFVIIa has been associated with thromboembolic events.</li><li>• For patients with a history of HIT use 3-factor PCC without heparin<sup>§</sup> (Factor IX complex).</li></ul>

§ Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

Note: All recommendations are category 2A unless otherwise indicated.

[References on VTE-K 8 of 8](#)



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### ANDEXANET ALFA DOSING AND ADMINISTRATION

Table 1: Andexanet Alfa Dosing Strategy <sup>§</sup>			
Medication	Last Dose	Dosing Strategy Based on Time Since Last Dose	
		Last Dose <8 Hours Prior or Unknown	Last Dose ≥8 Hours Prior
Rivaroxaban	≤10 mg	Low-dose	Low-dose
	>10 mg or unknown	High-dose	Low-dose
Apixaban	≤5 mg	Low-dose	Low-dose
	>5 mg or unknown	High-dose	Low-dose
Edoxaban	≤30 mg	Low-dose	Low-dose
	>30 mg	High-dose	Low-dose

Table 2: Andexanet Alfa Low- and High-Dose Strategies and Administration Instructions <sup>§</sup>		
Dose*	Initial IV Bolus (administered at a rate of 30 mg/min)	IV Infusion
Low-dose	400 mg	480 mg administered over 120 minutes (4 mg/min)
High-dose	800 mg	960 mg administered over 120 minutes (8 mg/min)

<sup>§</sup> Refer to package insert for full prescribing information: <https://www.accessdata.fda.gov/scripts/cder/daf/>

\* All patients should receive an initial IV bolus followed immediately by IV infusion as outlined above. The safety and efficacy of repeat dosing or extension of infusion beyond this time frame have not been evaluated.

**Note: All recommendations are category 2A unless otherwise indicated.**

[References on VTE-K 8 of 8](#)



# NCCN Guidelines Version 3.2025

## Cancer-Associated Venous Thromboembolic Disease

### REVERSAL OF ANTICOAGULATION REFERENCES

The preceding tables are comprised of data from the following references:

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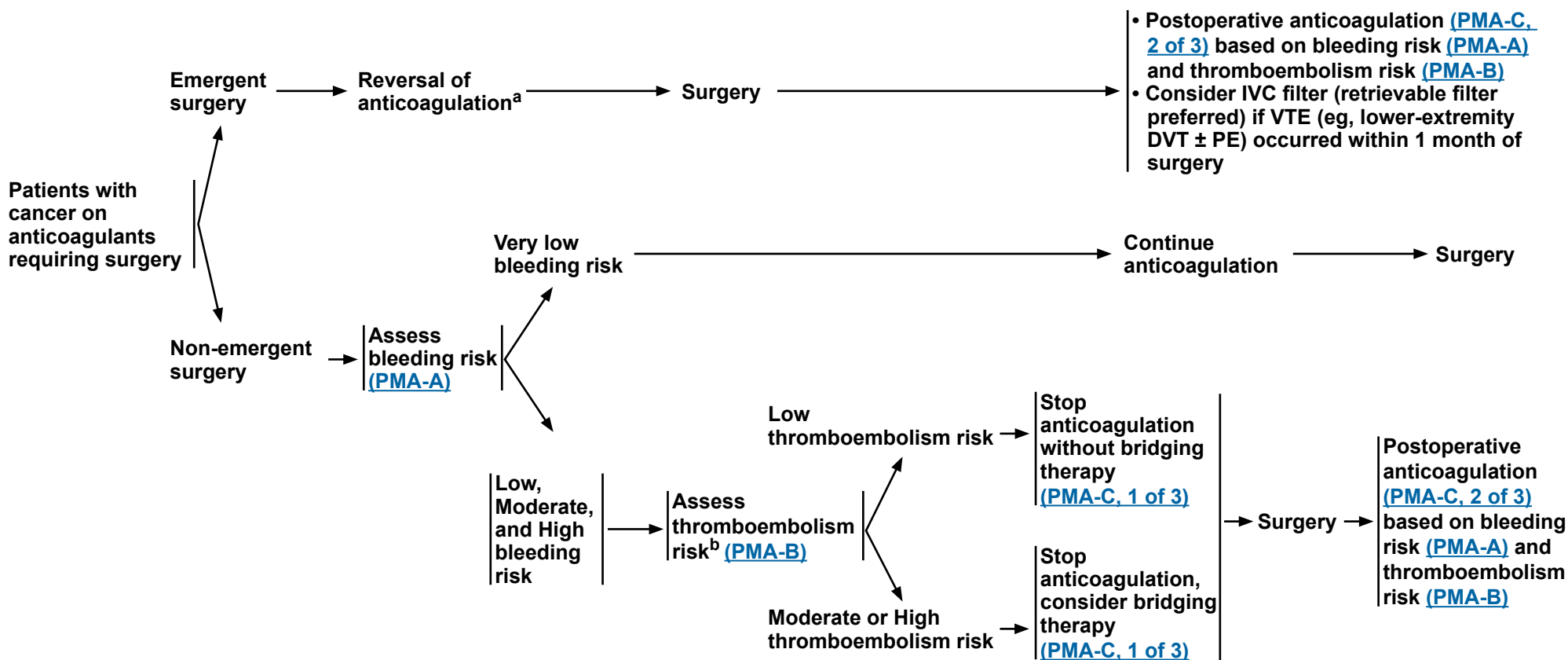


## Perioperative Management of Anticoagulation and Antithrombotic Therapy

### POPULATION AT RISK

### BLEEDING RISK ASSESSMENT

### THROMBOEMBOLISM RISK ASSESSMENT



<sup>a</sup> [Reversal of Anticoagulation \(VTE-K 1 of 8\)](#).

<sup>b</sup> Consider IVC filter (retrievable filter preferred) if VTE (eg, lower-extremity DVT ± PE) occurred within 1 month of surgery. Patient should be assessed periodically for filter retrieval once anticoagulation is safely resumed.

**Note: All recommendations are category 2A unless otherwise indicated.**



# Perioperative Management of Anticoagulation and Antithrombotic Therapy

## BLEEDING RISK ASSESSMENT

Patients with cancer frequently undergo invasive procedures as part of their treatment. Many patients with cancer are on anticoagulation. Patients with cancer are at increased risk for bleeding and thrombotic complications. The purpose of this section is to provide guidance to clinicians caring for patients with cancer on anticoagulation who are scheduled for an invasive procedure.

- Step 1: Assess the bleeding risk of the procedure (Table 1) and the patient's risk for thromboembolism (Table 2, [PMA-B](#)).
- Step 2: Determine whether anticoagulation needs to be held and the duration of anticoagulation interruption ([PMA-C 1 of 3](#)).
- Step 3: Determine if bridging anticoagulation is appropriate ([PMA-C 2 of 3](#)).
- Step 4: Determine when therapeutic anticoagulation can be resumed post-procedure ([PMA-C 2 of 3](#)).

Table 1: Bleeding Risk Associated with Different Invasive Procedures

Bleeding Risk Category	Type of Surgery or Procedure			
High	<ul style="list-style-type: none"><li>• Neurosurgical procedure (intracranial or spinal)</li><li>• Cardiac surgery</li><li>• Urologic surgery</li></ul>			
Moderate	<ul style="list-style-type: none"><li>• Major vascular surgery (abdominal aortic aneurysm [AAA] repair, peripheral artery bypass)</li><li>• Reconstructive plastic surgery</li><li>• Major orthopedic surgery</li><li>• Head and neck surgery</li><li>• Bronchoscopy with biopsy</li><li>• Biopsy (prostate, bladder, kidney, liver, thyroid, lymph node)</li></ul>	<ul style="list-style-type: none"><li>• Major intra-abdominal surgery</li><li>• Major intra-thoracic surgery</li><li>• GI endoscopy (esophagogastroduodenoscopy [EGD], enteroscopy, flexible sigmoidoscopy, colonoscopy) with polypectomy</li><li>• GI laser ablation and coagulation</li><li>• Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy</li><li>• Pneumatic or bougie dilation of benign or malignant strictures</li></ul>	<ul style="list-style-type: none"><li>• Endoscopic US (EUS) fine-needle aspiration (FNA)</li><li>• Endoscopy with esophageal variceal band ligation/gastric variceal ligation</li><li>• Laparoscopic cholecystectomy or hernia repair</li><li>• Percutaneous endoscopic gastrostomy (PEG) tube placement</li><li>• Spinal injections</li></ul>	
Low	<ul style="list-style-type: none"><li>• Core needle breast biopsy</li><li>• Coronary angiography and right heart catheterization (including biopsy)</li><li>• Arthroscopy</li></ul>	<ul style="list-style-type: none"><li>• Central venous catheter placement</li><li>• Bone marrow biopsy</li><li>• Pacemaker or automatic implantable cardioverter defibrillator (AICD) placement</li><li>• Arteriovenous (AV) fistula placement</li></ul>	<ul style="list-style-type: none"><li>• Lumbar puncture</li><li>• GI endoscopy (EGD, enteroscopy, flexible sigmoidoscopy, colonoscopy) with biopsy</li></ul>	
Very low	<ul style="list-style-type: none"><li>• Minor dermatologic procedures (skin biopsy, excisions of basal and squamous cell carcinomas, actinic keratoses, and malignant or premalignant nevi)</li><li>• Cataract removal</li><li>• Electroconvulsive therapy (ECT)</li><li>• IVC filter placement or removal</li><li>• Arthrocentesis</li></ul>	<ul style="list-style-type: none"><li>• Joint or soft tissue injections</li><li>• Endovascular ablation for varicose veins</li><li>• GI endoscopy (EGD, push enteroscopy, flexible sigmoidoscopy, colonoscopy) without biopsy or polypectomy</li><li>• ERCP without sphincterotomy</li><li>• Biliary/pancreatic stent insertion without endoscopic sphincterotomy</li><li>• EUS without FNA</li><li>• Push enteroscopy</li></ul>	<ul style="list-style-type: none"><li>• Minor dental procedures<sup>a</sup><ul style="list-style-type: none"><li>▸ Subgingival scaling</li><li>▸ Restorations with subgingival preparations</li><li>▸ Standard root canal therapy</li><li>▸ Simple extractions of one or more teeth</li></ul></li><li>• Regional injection of local anesthetics</li><li>• Standard dental cleanings or cavity fillings</li></ul>	

<sup>a</sup> Use of local hemostatic agents such as topical tranexamic acid and aminocaproic acid or thrombin-soaked absorbable gelatin powder is encouraged in the event of bleeding.

Note: All recommendations are category 2A unless otherwise indicated.

[References on PMA-C 3 of 3](#)





## Perioperative Management of Anticoagulation and Antithrombotic Therapy

### THROMBOEMBOLIC RISK ASSESSMENT FOR ARTERIAL THROMBOEMBOLISM AND VTE

Table 2: Thromboembolic Risk Categories

Risk Category	Clinical Conditions
High Thromboembolic Risk	<ul style="list-style-type: none"><li>• Mitral mechanical valve (bileaflet)</li><li>• Single-leaflet or caged-ball mechanical valve</li><li>• Mechanical valve with recent stroke (&lt;3 months)</li><li>• Atrial fibrillation (CHADSVasc ≥7)</li><li>• Atrial fibrillation with recent stroke (&lt;3 months)</li><li>• Recent embolic stroke (&lt;3 months)</li><li>• VTE within 3 months</li><li>• High-risk inherited thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, homozygous Factor V Leiden or prothrombin gene mutation, compound heterozygous Factor V Leiden/prothrombin gene mutation or other combined thrombophilic defects [eg, Factor V Leiden + protein C deficiency])</li><li>• APS</li><li>• Active high thrombotic risk cancer<sup>a</sup> with previous thromboembolism</li></ul>
Moderate Thromboembolic Risk	<ul style="list-style-type: none"><li>• Aortic mechanical valve (bileaflet) with atrial fibrillation or prior stroke (&gt;3 months)</li><li>• Atrial fibrillation (CHADSVasc 5–6)</li><li>• VTE in last 3–12 months</li><li>• Factor V Leiden or prothrombin gene mutation heterozygosity</li><li>• Active non-high thrombotic risk cancer<sup>a</sup> with previous thromboembolism</li></ul>
Low Thromboembolic Risk	<ul style="list-style-type: none"><li>• Aortic mechanical valve (bileaflet) without atrial fibrillation or prior stroke</li><li>• Atrial fibrillation (CHADSVasc &lt;5)</li><li>• VTE &gt;12 months</li></ul>

<sup>a</sup> High thrombotic risk cancers include pancreatic, liver, biliary, lung, stomach, brain, and esophageal cancers. Non-high thrombotic risk cancers include all other cancers, excluding non-melanoma skin cancer. Mulder FI, et al. Blood 2021;137:1959-1969.

**Note: All recommendations are category 2A unless otherwise indicated.**

[References on PMA-C 3 of 3](#)



## Perioperative Management of Anticoagulation and Antithrombotic Therapy

### PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH CANCER

For high and moderate bleeding risk procedures, the Panel recommends holding anticoagulation as outlined in Tables 3–4.

For low bleeding risk procedures, anticoagulation is often held according to the schedule in Tables 3–4, although practice varies with the procedure, anticoagulant, and institution. Some institutions hold anticoagulation for bone marrow biopsy while others continue anticoagulation depending upon the medication (ie, DOAC, warfarin, heparin). Pacemaker or AICD placement is routinely done on warfarin without interruption, but practice varies with DOACs. Anticoagulation is held for spinal injections and lumbar puncture.

For very low bleeding risk procedures, the panel recommends continuation of anticoagulation in most instances. Follow institutional SOPs, if available.

**Table 3: Periprocedural Management of Oral Anticoagulants: Hold Times**

Medication	Renal Function	Low Bleeding Risk Procedure	High/Moderate Bleeding Risk Procedure
Apixaban	CrCl ≥30 mL/min	2 days (4 doses)	3 days (6 doses)
	CrCl <30 mL/min	3 days (6 doses)	3–4 days (6–8 doses)
Dabigatran	CrCl ≥50 mL/min	2 days (4 doses)	3 days (6 doses)
	CrCl 30–49 mL/min	3 days (6 doses)	4 days (8 doses)
Edoxaban	CrCl ≥30 mL/min	2 days (2 doses)	3 days (3 doses)
Rivaroxaban	CrCl ≥30 mL/min	2 days (2 doses)	3 days (3 doses)
Warfarin	Not relevant	5 days <sup>a</sup>	5 days (INR 2–3)
			>5 days (INR >3) <sup>b</sup>

**Table 4: Periprocedural Management of Parenteral Anticoagulants: Hold Times**

Medication	Dosage	Renal Function	Low Bleeding Risk Procedure	High/Moderate Bleeding Risk Procedure
Enoxaparin (Half-life 4.5–7 hours)	1 mg/kg every 12 hours	CrCl >50 mL/min	12–24 hours (1–2 doses)	24 hours (2 doses)
	0.8 mg/kg every 12 hours	CrCl 30–50 mL/min	24 hours (2 doses)	24–36 hours (2–3 doses)
	1 mg/kg every 24 hours	CrCl <30 mL/min	24 hours (1 dose)	24–48 hours (1–2 doses)
Fondaparinux (Half-life 17–21 hours)	5 mg every 24 hours for body weight <50 kg	CrCl ≥50 mL/min	84 hours (4 doses)	105–126 hours (5–6 doses)
	7.5 mg every 24 hours for body weight 50–100 kg			
	10 mg every 24 hours for body weight >100 kg			

<sup>a</sup> Some low-risk procedures are performed preferably without warfarin discontinuation (eg, pacemaker or AICD). Other low bleeding risk procedures may not require 5-day interruption (advise discussion with interventionalist).

<sup>b</sup> Patients with a target goal or pre-procedure INR >3 may require more than 5 days of interruption for normal hemostasis. Suggest pre-procedure INR assessment to determine hold time if feasible.

**Note:** All recommendations are category 2A unless otherwise indicated.

[References on PMA-C 3 of 3](#)

**PMA-C**  
**1 OF 3**



## Perioperative Management of Anticoagulation and Antithrombotic Therapy

### PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH CANCER

#### Pre-procedural Bridging Anticoagulation

- For patients taking warfarin, the majority of NCCN Member Institutions consider bridging anticoagulation for patients at high risk of thromboembolism. A minority consider bridging anticoagulation for patients at moderate or high thromboembolic risk. A smaller minority consider bridging anticoagulation for patients only at exceptionally high risk (eg, recent VTE or stroke <1 month, previous episode of thromboembolism in a perioperative period without bridging). The panel does not recommend bridging anticoagulation for patients at low thromboembolic risk.
- For most patients taking DOACs, bridging anticoagulation is not necessary since the duration of interruption is shorter than warfarin. The majority of institutions reported considering bridging anticoagulation only for select DOAC recipients at exceptionally high risk of thromboembolism (eg, recent VTE or stroke <1 month, previous episode of thromboembolism in the perioperative period without bridging). A minority reported that they do not consider bridging anticoagulation for any patients taking DOACs. Smaller minorities of institutions consider bridging anticoagulation for patients at high thromboembolic risk or for patients at moderate or high risk of thromboembolism.

#### Post-procedural Resumption of Anticoagulation

- All patients should receive standard VTE thromboprophylaxis once hemostasis is adequate (generally within 12–24 hours postoperatively). VTE prophylaxis can be continued until therapeutic dose anticoagulation is resumed.
- For low bleeding risk procedures, therapeutic anticoagulation can generally be resumed ≥24 hours postoperation if hemostasis is adequate. Since warfarin takes several days to reach therapeutic concentrations, the majority of institutions recommend resumption of warfarin on the night of surgery after a low bleeding risk procedure. A majority also recommended resumption of therapeutic-dose LMWH, DOACs, or fondaparinux on POD1.
- For moderate bleeding risk procedures, resumption of therapeutic anticoagulation may be considered 48–72 hours post-procedure if hemostasis is adequate. Since warfarin takes several days to reach therapeutic concentrations, the majority of institutions recommend resumption of warfarin on POD1. A minority recommend resumption on POD2–3. The majority of NCCN Member Institutions recommend resumption of therapeutic-dose LMWH, DOACs, or fondaparinux on POD2 after a moderate bleeding risk procedure. A minority recommend resumption on POD3.
- For high bleeding risk procedures, resumption of therapeutic anticoagulation may be considered ≥72 hours post-procedure depending upon hemostasis. Warfarin may be resumed in the first 24–48 hours since it takes several days to reach therapeutic concentrations and the majority of institutions recommend resumption of warfarin on POD2. The majority of institutions recommend resumption of therapeutic-dose LMWH, DOACs, or fondaparinux on POD3 after a high bleeding risk procedure, although a minority recommend resumption on either POD2 or on POD4 or later.

#### Limitations and Important Considerations

- This section is based upon the Panel's assessment of the current literature on perioperative anticoagulation management in patients with cancer. There were considerable differences of opinions on management in many areas, which reflects the limited information on perioperative outcomes in patients with cancer on anticoagulation, who are likely to be at higher bleeding and thrombotic risk compared to patients without cancer. Since the risk of perioperative bleeding or thrombosis can be influenced by a large number of variables, including but not limited to the patient's cancer site and stage, proposed invasive procedure, antithrombotic medications, and concurrent medical conditions, periprocedural anticoagulation management should be determined on a case-by-case basis. For optimal outcomes, it is essential to develop a perioperative anticoagulation plan in advance in conjunction with the patient's proceduralist.

Note: All recommendations are category 2A unless otherwise indicated.

#### [References on PMA-C 3 of 3](#)



## Perioperative Management of Anticoagulation and Antithrombotic Therapy

### PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION IN PATIENTS WITH CANCER REFERENCES

The preceding pages are comprised of data from the following references:

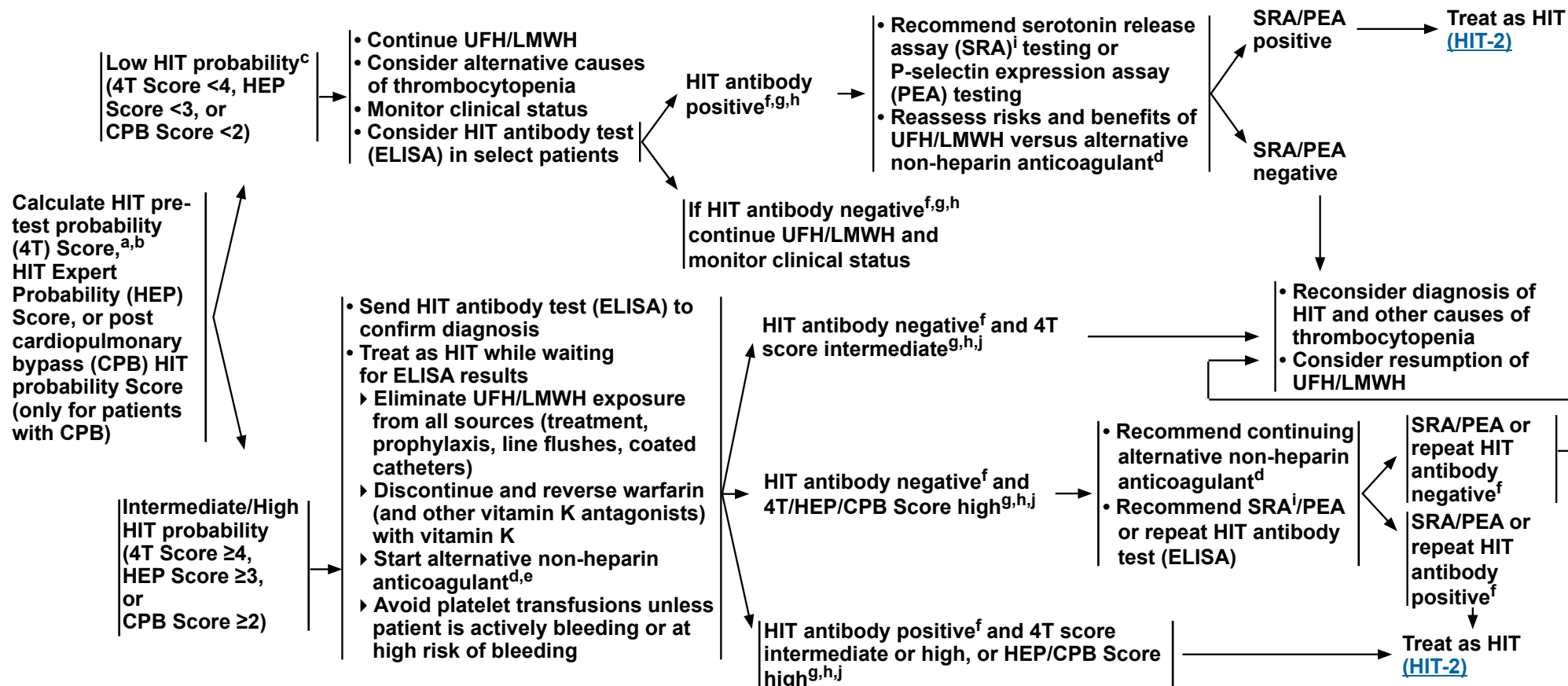
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**Note: All recommendations are category 2A unless otherwise indicated.**

# NCCN Guidelines Version 3.2025

## Heparin-Induced Thrombocytopenia

### WORKUP AND MANAGEMENT FOR SUSPECTED HIT



<sup>a</sup> See [HIT-A](#) for HIT Probability Assessment Tools.

<sup>b</sup> The 4T score has not been validated in patients with cancer, so it may have less utility, particularly in patients receiving chemotherapy who have alternative causes for thrombocytopenia.

<sup>c</sup> A “low” pre-test probability score combined with a negative antibody test is useful in ruling out a diagnosis of HIT; a positive test increases the suspicion for HIT. In patients without cancer with 4T scores of 1–3, the risk of HIT is small but not zero, but this has not been validated in patients with cancer. Based on clinical judgment, HIT antibody testing and initiation of argatroban/bivalirudin or fondaparinux in place of UFH/LMWH may be warranted in select patients.

<sup>d</sup> [Initial Treatment for Suspected or Confirmed HIT \(HIT-2\)](#).

<sup>e</sup> For patients without an indication for therapeutic anticoagulation who are judged to be at high risk of bleeding and moderate risk of HIT, a prophylactic dose of a non-heparin anticoagulant could be considered while awaiting the results of initial testing (Cuker A, et al. Blood Adv 2018;2:3360-3392).

<sup>f</sup> Cutoff for ELISA HIT antibody test may vary depending on the specific assay used.

<sup>g</sup> Cuker A, et al. Blood 2016;127:522-524.

<sup>h</sup> Nagler M, et al. Blood 2016;127:546-557.

<sup>i</sup> Consider institution-specific ELISA optical density (OD) value thresholds when determining whether to send SRA/PEA.

<sup>j</sup> 4T score: 0–3 low probability of HIT, 4–5 intermediate probability of HIT, 6–8 high probability of HIT; HEP score: 1st cutoff: ≥2 positive for HIT, <2 negative for HIT (sensitivity 1.00 [0.56–1.00], specificity 0.60 [0.45–0.75]); 2nd cutoff: ≥5 positive for HIT, <5 negative for HIT (sensitivity 0.86 [0.42–0.99], specificity 0.88 [0.74–0.96]); CPB score: <2 low probability of HIT, ≥2 high probability of HIT.

**Note: All recommendations are category 2A unless otherwise indicated.**





# NCCN Guidelines Version 3.2025

## Heparin-Induced Thrombocytopenia

### TREATMENT FOR HIT

- Global assessment of bleeding and clotting should be performed prior to treatment.

#### Initial Treatment for Patients with Suspected or Confirmed HIT

- Start/continue alternative non-heparin anticoagulant
  - There are no data from randomized controlled trials comparing different non-heparin anticoagulants to inform anticoagulant selection for treatment of HIT (with or without thrombosis). Therefore, an IV direct thrombin inhibitor (DTI) is preferred for initial treatment of hospitalized patients with suspected HIT (ie, patients awaiting test results) or confirmed HIT, as many of these patients are critically ill and have contraindications to fondaparinux or DOACs.<sup>k</sup>
  - DOACs or fondaparinux are considered reasonable options for the initial treatment of patients who are clinically stable without hemodynamically unstable PE or limb-threatening thrombosis or planned invasive procedures who do not have contraindications to the use of these agents as listed on [VTE-D, 4 of 7](#).<sup>l</sup>
  - Full-dose anticoagulation is generally preferred, depending on assessment of bleed and clot risks.
  - For more information on agent selection and dosing, see [Therapeutic Options for HIT \(HIT-B\)](#).

#### Additional Recommendations for Patients with Confirmed HIT

- Lower-extremity US is recommended to identify asymptomatic DVT; consider upper-extremity US based on clinical situation.
- For patients who are stabilized on initial HIT treatment and have no procedures planned, consider transitioning to an alternative agent:
  - DOACs (preferred): For patients with adequate renal and hepatic function and no other contraindications (listed on [VTE-D, 2 of 6](#))
  - Fondaparinux
  - Warfarin
  - For more information on agent selection and administration, see [Therapeutic Options for HIT \(HIT-B\)](#).
- Intravenous immunoglobulin has been shown to be effective in patients with refractory HIT as well as autoimmune HIT. It is also a useful treatment for patients at high risk of bleeding who have HIT.
- Duration of therapy:
  - HIT without thrombosis: At least 4 weeks (in the absence of serious bleeding risk)
  - HIT with thrombosis: At least 3 months as indicated for thrombotic event

<sup>k</sup> Opinions vary among Panel members regarding the quality of data supporting treatment options for the management of HIT in patients with cancer.

<sup>l</sup> Among the DOAC options listed for the management of HIT, rivaroxaban is supported by the most data, but there is no evidence to suggest that other DOAC options are not equally effective. Due to the lack of data, caution is recommended when using DOACs for management of HIT in patients with cancer.

**Note: All recommendations are category 2A unless otherwise indicated.**





# NCCN Guidelines Version 3.2025

## Heparin-Induced Thrombocytopenia

### HIT PRE-TEST PROBABILITY SCORE ASSESSMENT TOOL<sup>a</sup>

Suspicion of HIT based on the “4 T’s”		HIT Pre-test Probability Score Criteria		
	Score	2	1	0
<u>T</u> hrombocytopenia	<input type="checkbox"/>	Nadir 20,000–100,000/ $\mu$ L or >50% platelet fall	Nadir 10,000–19,000/ $\mu$ L or 30%–50% platelet fall	Nadir <10,000/ $\mu$ L or <30% platelet fall
<u>T</u> iming of onset platelet fall (days of heparin therapy)	<input type="checkbox"/>	Days 5–10 or $\leq$ day 1 with recent heparin <sup>b</sup>	> day 10 or timing unclear (but fits with HIT)	$\leq$ day 1 (no recent heparin)
<u>T</u> hrombosis or other sequelae	<input type="checkbox"/>	Proven thrombosis, skin necrosis, or ASR <sup>c</sup>	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
<u>O</u> ther cause of platelet fall	<input type="checkbox"/>	None evident	Possible	Definite
Total Pre-test Probability Score	<input type="checkbox"/>	Periodic reassessment as new information can change pre-test probability (eg, positive blood cultures)		

### Total HIT Pre-test Probability Score

High			Moderate		Low			
8	7	6	5	4	3	2	1	0

<sup>a</sup> Modified with permission from Warkentin TE, Aird WC, Rand JH. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2003;497-519.

<sup>b</sup> Recent heparin indicates exposure within the past 30 days (2 points) or past 30–100 days (1 point).

<sup>c</sup> Acute systemic reaction (ASR) following IV heparin bolus.

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Heparin-Induced Thrombocytopenia

### HIT EXPERT PROBABILITY (HEP) SCORE<sup>d,e</sup>

Clinical Features	Points
1. Magnitude of fall in platelet count (measured from peak platelet count to nadir platelet count since heparin exposure)	
<30%	-1
30%–50%	1
>50%	3
2. Timing of fall in platelet count	
For patients in whom typical onset HIT is suspected	
Fall begins <4 days after heparin exposure	-2
Fall begins 4 days after heparin exposure	2
Fall begins 5–10 days after heparin exposure	3
Fall begins 11–14 days after heparin exposure	2
Fall begins >14 days after heparin exposure	-1
For patients with heparin exposure in past 100 days in whom rapid onset HIT is suspected	
Fall begins ≤48 hours after heparin re-exposure	2
Fall begins >48 hours after heparin re-exposure	-1
3. Nadir platelet count	
≤ 20 x 10 <sup>9</sup> /L	-2
> 20 x 10 <sup>9</sup> /L	2

NOTE: <3 is negative; ≥3 is positive

<sup>d</sup> Reproduced with permission from Cuker A. Clinical and laboratory diagnosis of heparin-Induced thrombocytopenia: An integrated approach. Semin Thromb Hemost 2014;40:106-114. © Georg Thieme Verlag KG.

<sup>e</sup> See HEP calculator accessible at <https://www.mdcalc.com/hit-expert-probability-hep-score-heparin-induced-thrombocytopenia>.

**Note: All recommendations are category 2A unless otherwise indicated.**

# NCCN Guidelines Version 3.2025

## Heparin-Induced Thrombocytopenia

### SCORE FOR PATIENTS WITH PRIOR CPB<sup>f</sup>

Variables	Score
Platelet count time course	
Pattern A <sup>g</sup>	2
Pattern B <sup>h</sup>	1
Time from CPB to index date	
≥5 days	2
<5 days	0
CPB duration	
≤118 min	1
>118 min	0
Total Score	
Classification	
High probability of HIT	≥2
Low probability of HIT	<2

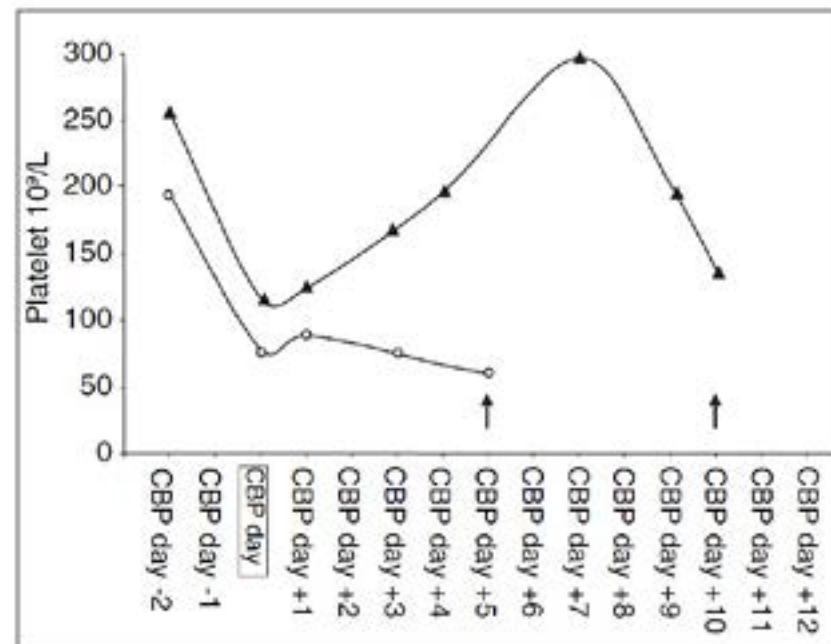


Figure 1 - Example of platelet time courses from 2 distinct patients. Representation of one pattern A (biphasic pattern, solid triangles), characterized by a fall in the platelet count more than 4 days after CPB (the initial fall immediately after CPB is followed by a rise within 5 days and then by a further fall) and one pattern B (open circles), characterized by post-CPB thrombocytopenia persisting beyond day 4. Platelet counts are reported until the index date (first day of suspected HIT, arrows).

<sup>f</sup> Reproduced with permission from Lillo-Le Louët A, Boutouyrie P, Alhenc-Gelas M, et al. Diagnostic score for heparin-induced thrombocytopenia after cardiopulmonary bypass. J Thromb Haemost 2004;2:1882-1888.

<sup>g</sup> Pattern A: platelet count fall >4 days after CPB; usually biphasic, with an initial fall immediately after CPB, followed by a rise of ≥30% within 5 days and then by a further fall.

<sup>h</sup> Pattern B: thrombocytopenia occurring immediately after CPB and persisting or worsening for >4 days (or before in case of previous heparin treatment).

**Note: All recommendations are category 2A unless otherwise indicated.**



# NCCN Guidelines Version 3.2025

## Heparin-Induced Thrombocytopenia

### THERAPEUTIC OPTIONS FOR HIT<sup>a</sup>

#### DOACs

- Options: apixaban, rivaroxaban, dabigatran (category 2B), edoxaban (category 2B)
- Rarely used for initial treatment of HIT; may be a reasonable option for patients who have stabilized on initial treatment for HIT (DTI or fondaparinux), have no procedures planned, and have no contraindications (listed on [VTE-D, 4 of 7](#)). There are limited data to support the use of DOACs in patients with HIT.
  - ▶ For patients transitioning from DTI to DOAC: If DTI is in the therapeutic range, stop DTI and give the first dose of DOAC at the same time.
  - ▶ For patients transitioning from fondaparinux to DOAC: Give the first dose of DOAC instead of fondaparinux at the next scheduled administration time for fondaparinux.

#### Indirect Factor Xa Inhibitor<sup>b</sup>

- Fondaparinux (half-life 17–21 h with normal renal function)
  - ▶ For patients with CrCl 30–50 mL/min (clearance reduced by 40%): Consider using a DTI<sup>c</sup>
  - ▶ For patients with CrCl <30 mL/min: Avoid fondaparinux
  - ▶ Dosing
    - ◊ Body weight <50 kg: 5 mg SC daily
    - ◊ Body weight 50–100 kg: 7.5 mg SC daily
    - ◊ Body weight >100 kg: 10 mg SC daily

#### DTIs

- Argatroban (half-life 45 min with normal liver function; aPTT 1.5–3x initial baseline value not to exceed 100 sec)<sup>c</sup>
  - ▶ Normal liver function, non-intensive care unit (ICU) status: 2 mcg/kg/min adjusted to aPTT ratio (first check in 4 h)
  - ▶ Abnormal liver function (total bilirubin, 1.8–3.6 mg/dL; AST/ALT, 150–600 IU/L) or ICU status, patient with cardiac conditions, or patient with multi-organ failure: 0.5 mcg/kg/min
  - ▶ Severe liver dysfunction (total bilirubin, >3.6 mg/dL or AST/ALT, >600 IU/L): Use bivalirudin or fondaparinux

- Bivalirudin (half-life 25 minutes with normal renal function; aPTT 1.5–2.5x initial baseline value)<sup>d,1</sup>
  - ▶ Strongly consider for patients with combined hepatic and renal dysfunction
  - ▶ Dosing
    - ◊ Estimated CrCl >60 mL/min: 0.15 mg/kg/h – adjust to aPTT (first check 2 h)
    - ◊ Estimated CrCl 45–60 mL/min: 0.1 mg/kg/h
    - ◊ Estimated CrCl 31–44 mL/min: 0.075 mg/kg/h
    - ◊ Estimated CrCl <30 mL/min (no renal replacement therapy): 0.05 mg/kg/h
    - ◊ Renal replacement therapy or combined hepatic/renal failure: Consider argatroban for isolated renal failure or use 0.04 mg/kg/h

#### Platelet Transfusions

- Avoid unless active bleeding or invasive procedure necessary and platelet count <50,000/μL

#### Warfarin

- Initiate once platelet count ≥150,000/μL or return to baseline
- Initial dose 5 mg (consider lower dose for patients: age >75 years, CYP2C9 inhibitors, poor oral intake, liver disease)
- DTIs, particularly argatroban, can increase the INR substantially during warfarin co-therapy; therefore, a higher target INR (approximately 4.0) should be achieved before DTI therapy is discontinued. Bivalirudin slightly prolongs the INR during co-therapy.
- Discontinue DTI or fondaparinux after at least 5 to 7 days overlap and when the INR reaches intended target range (≥2).
- INR and aPTT should be repeated within 2 to 6 hours after DTI has been discontinued to ensure the INR is still therapeutic when the effects of DTI are no longer present.
- If available, chromogenic factor X activity, which is not affected by DTIs, can be used to monitor warfarin during co-therapy.

#### Intravenous Immunoglobulin (refractory HIT, autoimmune HIT, or patients at high risk of bleeding who have HIT)

- 1 g/kg IV daily x2

<sup>1</sup> Joseph L, Casanegra AI, Dhariwal M, et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. *J Thromb Haemost* 2014;12:1044-1053.

<sup>a</sup> The NCCN Guidelines Panel encourages the development of protocols or order sets for HIT treatment that includes DTI dosing, adjustment in renal or hepatic dysfunction, nursing instructions, and monitoring parameters.

<sup>b</sup> Used as a second-line agent. Fondaparinux has been rarely associated with HIT.

<sup>c</sup> See most recent prescribing information at: <https://www.accessdata.fda.gov/scripts/cder/daf/>.

<sup>d</sup> Anaphylaxis has occurred with bivalirudin.

**Note: All recommendations are category 2A unless otherwise indicated.**



### ABBREVIATIONS

AAA	abdominal aortic aneurysm	ERCP	endoscopic retrograde cholangiopancreatography	PEA	P-selectin expression assay
ACCP	American College of Chest Physicians	EUS	endoscopic ultrasound	PEG	percutaneous endoscopic gastrostomy
AICD	automatic implantable cardioverter defibrillator	FFP	fresh frozen plasma	P-gp	P-glycoprotein
ALT	alanine aminotransferase	FNA	fine-needle aspiration	PICC	peripherally inserted central catheter
aPCC	activated prothrombin complex concentrate	GCS	graduated compression stockings	PNH	paroxysmal nocturnal hemoglobinuria
APS	antiphospholipid syndrome	GI	gastrointestinal	POC	point-of-care
aPTT	activated partial thromboplastin time	H&P	history and physical	POD	postoperative day
ASR	acute systemic reaction	HEP	HIT expert probability	PT	prothrombin time
AST	aspartate aminotransferase	HIT	heparin-induced thrombocytopenia	PTS	post-thrombotic syndrome
AV	arteriovenous	ICU	intensive care unit	RAM	risk assessment model
BMI	body mass index	INR	international normalized ratio	RBC	red blood cell
CBC	complete blood count	IPC	intermittent pneumatic compression	RYGB	Roux-en-Y gastric bypass
CPB	cardiopulmonary bypass	IVC	inferior vena cava	rhFVIIa	recombinant human coagulation Factor VIIa
CrCl	creatinine clearance	LMWH	low-molecular-weight heparin	SOP	standard operating procedure
CTA	computed tomography angiography	LV	left ventricular	SPVT	splanchnic vein thrombosis
CTV	CT venogram	MHN	myeloproliferative neoplasm	SRA	serotonin release assay
CVAD	central venous access device	MRA	magnetic resonance angiography	SVC	superior vena cava
DOAC	direct oral anticoagulant	MRV	magnetic resonance venogram	SVT	superficial vein thrombosis
DTI	direct thrombin inhibitor	NSAID	nonsteroidal anti-inflammatory drug	TIPS	transjugular intrahepatic portosystemic shunt
dTT	diluted thrombin time	NT-proBNP	N-terminal prohormone B-type natriuretic peptide	UFH	unfractionated heparin
DVT	deep vein thrombosis	OD	optical density	ULN	upper limit of normal
ECG	electrocardiogram	OR	operating room	VA-ECMO	venoarterial extracorporeal membrane oxygenation
ECT	electroconvulsive therapy	PCC	prothrombin complex concentrate	VTE	venous thromboembolism
EGD	esophagogastroduodenoscopy	PE	pulmonary embolism	VQ	ventilation/perfusion



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NCCN Categories of Evidence and Consensus	
<b>Category 1</b>	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
<b>Category 2A</b>	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
<b>Category 2B</b>	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
<b>Category 3</b>	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
<b>Preferred intervention</b>	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
<b>Other recommended intervention</b>	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
<b>Useful in certain circumstances</b>	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.





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### Discussion

This discussion corresponds to the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease. Last updated: November 6, 2025.

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### Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in patients with cancer.<sup>1</sup> Results from a 2021 population-based cohort study showed that the presence of cancer increased the risk of VTE by 9-fold.<sup>2</sup> In a health claims database analysis of patients with cancer undergoing chemotherapy, VTE occurred in 12.6% of patients during the 12-month period from initiation of chemotherapy, compared with a rate of 1.4% among an age- and gender-matched control cohort without cancer.<sup>3</sup> Chemotherapy, anti-angiogenic therapy, protein kinase inhibitors, and immunotherapy have all been shown to increase the risk of VTE.<sup>2</sup> More importantly, thrombosis is a leading cause of death in patients with cancer, found to be second only to cancer itself in a large prospective observational study.<sup>4</sup> Multiple studies have reported significantly higher mortality and reduced overall survival among patients with cancer who developed VTE compared to those who did not.<sup>5-10</sup> Specifically, the occurrence of VTE has been reported to increase the likelihood of death for patients with cancer by 2- to 6-fold.<sup>8-12</sup> VTE has been reported to be the most common cause of death at 30-day follow-up among patients with cancer undergoing surgery.<sup>13</sup>

The underlying etiology of cancer-associated VTE is multifaceted and attributable to patient-related, cancer-related, and treatment-related factors. Stratification of these factors and accurate identification of patients with cancer at risk of developing VTE are important to prevent potentially deadly complications. It has also been acknowledged that patients with medical and surgical oncology needs, both hospitalized and ambulatory, are at increased risk of developing VTE.<sup>1,3,5,14,15</sup> Therefore, appropriate use of VTE prophylaxis can bring about substantial benefits in patients at risk.<sup>16,17</sup> The different subtypes of VTE, despite sharing similarities, can have vastly different symptoms and prognoses, requiring customized management plans with suitable diagnostic tools and therapeutics.<sup>18-22</sup> There are many treatment options for VTE, encompassing anticoagulants,

thrombolytics, mechanical devices, and surgical procedures, each with their own pros and cons.<sup>16,23</sup> Careful selection of treatment methods with the optimal efficacy to safety consideration is instrumental in achieving the best outcomes. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Associated Venous Thromboembolic Disease outline iterative implementations of therapeutic measures based on risk assessment, diagnoses of VTE subtypes, contraindications to therapeutic interventions, and cancer and treatment status of the patient.

### Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines® are available at [www.NCCN.org](http://www.NCCN.org).

### Literature Search Criteria

Prior to the update of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease, an electronic search of the PubMed database was performed to obtain key literature in Cancer-Associated Venous Thromboembolic Disease since the previous Guidelines update, using the following search terms: cancer-associated venous thromboembolism and cancer thrombosis. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.<sup>24</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; Multicenter Studies; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel have been included in this version of the Discussion section.



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Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

### Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

### VTE Risk Assessment in Patients with Cancer

VTE risk factors in patients with cancer can be grouped into three general categories: patient-related factors, cancer-related factors, and treatment-related factors. For an individual patient with cancer, VTE risk factors in all three categories are likely to be present, and the VTE risk conferred by a single risk factor cannot be evaluated in isolation from the others.

### Patient-Related Factors

Advanced age, a common characteristic of many patients with cancer, was shown to be associated with an increased risk for VTE in some clinical settings.<sup>6,13</sup> Obesity has also been identified as a risk factor for VTE.<sup>25-28</sup> Other modifiable risk factors for VTE are smoking/tobacco use and level of physical activity.<sup>29-34</sup> There might be confounding factors, such as other smoking-attributable diseases and higher body mass index (BMI), in the association between smoking and VTE.<sup>30,31</sup> Moreover, the relationship between level of physical activity and VTE is not straightforward, with multiple studies reporting a U-shaped association between the two entities.<sup>29,33,34</sup> A number of other patient-related VTE risk factors, although not exclusive to patients with cancer, are commonly found. These risk factors include familial and/or acquired hypercoagulability<sup>35,36</sup> (eg, strong thrombophilia such as antiphospholipid syndrome [APS],<sup>37,38</sup> pregnancy<sup>39-41</sup>) and other medical comorbidities, such as infection.<sup>42,43</sup> Although factor V Leiden and prothrombin gene 20210 mutations were identified in 3.7% and 2.6% of patients, respectively, with breast or colon cancer receiving adjuvant chemotherapy in a prospective observation study, these inherited risk factors were not associated with an increased risk for VTE among patients with cancer.<sup>44</sup>

With regard to medical comorbidities, a population-based study reported an estimated VTE incidence rate increase of 3-fold within the first 3 months after infection.<sup>43</sup> Other noteworthy independent risk factors for VTE development include renal disease,<sup>45-47</sup> pulmonary disease,<sup>48-51</sup> congestive heart failure (CHF),<sup>52,53</sup> and arterial thromboembolism.<sup>54-56</sup> A history of prior VTE has also been identified as an independent risk factor for developing a subsequent VTE.<sup>13,44,57-59</sup> Moreover, recurrent VTE was found to be more common among patients with cancer; for example, in a prospective follow-up study, 12-month cumulative incidences of recurrent VTE of 20.7% and 6.8% were reported for patients with and without cancer, respectively, receiving anticoagulant treatment.<sup>60</sup>

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Other patient-related characteristics that are considered major risk factors for VTE include hospitalization, prolonged immobilization, and poor performance status.<sup>61-63</sup> These factors can also be considered to be treatment-related if they result from cancer-related treatments. According to the U.S. Centers for Disease Control and Prevention (CDC), between 2007 and 2009, VTE was reported in >547,000 patients who were hospitalized annually, with >28,700 deaths.<sup>64</sup> Moreover, the risk for VTE increased with age in patients that were hospitalized. This report confirms that hospitalization is an important risk factor for VTE and emphasizes the need for greater awareness of VTE risks and appropriate implementation of preventive measures in this setting.

### Cancer-Related Factors

Several VTE risk factors are exclusive to patients with cancer, including the presence of malignancy and type and stage of cancer. As established in the *Overview*, cancer is a significant risk factor for VTE, and causes approximately 20% of VTE cases seen in the community.<sup>61</sup> Several studies have evaluated the association between types of cancer and the risk of developing VTE.<sup>1,3,6,8,65-67</sup> Pancreatic cancer<sup>3,6,8,65-68</sup> and brain tumors<sup>6,67,69</sup> are consistently associated with a high risk for VTE. It has been postulated that the tissue factor expression that occurs early in malignant transformation of the pancreas in association with angiogenesis may be predictive of VTE in pancreatic cancer.<sup>70,71</sup> Although differences in study designs make it difficult to compare VTE rates in a specific type of malignancy, other cancers that have been associated with an increased risk for VTE include cancers of the stomach, kidney, uterus, lung, ovary, bladder, and testes.<sup>1,3,6</sup> In contrast, breast cancer was associated with a relatively low VTE risk in some studies.<sup>9,72</sup> Nevertheless, due to the relatively high prevalence of breast cancer, VTE in patients with breast cancer is not uncommon.<sup>9,72</sup>

An increased risk for VTE has also been observed in certain hematologic malignancies, such as lymphoma, acute leukemia, and multiple myeloma (for guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma, available at [www.NCCN.org](http://www.NCCN.org)).<sup>6,73</sup> Notably, patients with high-grade lymphoma and acute promyelocytic leukemia appear to be at higher risk of VTE than patients with other forms of lymphoma or leukemia.<sup>74,75</sup> Furthermore, in a study of patients with high-grade non-Hodgkin lymphoma, disease-related venous compression was shown to be the most common cause of VTE.<sup>76</sup> Thus, the mechanisms for VTE development in hematologic malignancies can differ from those in solid tumors and are worth further investigation.

In addition, advanced disease stages and distant metastases increase VTE risk.<sup>1,67,68,77-79</sup> For example, Blom et al reported an adjusted odds ratio (OR) of 19.8 for VTE risk in patients with solid tumors with distant metastases compared to patients without distant metastases.<sup>1</sup> The strength of associations can differ substantially between cancer types, with the highest incidence rate difference for VTE according to stages reported for pancreatic cancer, and the lowest incidence rate difference reported for prostate cancer.<sup>79</sup>

### Treatment-Related Factors

Treatment-related VTE risk factors include major surgery, the presence of a central venous access device (CVAD), also known as a central venous catheter, and administration of systemic therapies. Heit et al reported a nearly 22-fold increase in the risk for VTE development in patients hospitalized for recent surgery compared with those who had not been hospitalized or who had not undergone recent surgery.<sup>61</sup> The overall 30-day VTE rate in patients with cancer after major surgeries ranges from 1.8% to 13.2%, with patients undergoing esophageal resection having the highest rate of 13.2% (95% CI, 8.8%–18.9%).<sup>80</sup> Importantly, a significant



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proportion of VTE episodes (34%) among patients admitted for surgical oncology care are diagnosed after hospital discharge, highlighting the importance of extended VTE prophylaxis in this patient population.<sup>81</sup>

CVADs have been identified as risk factors for the development of upper-extremity acute deep vein thrombosis (DVT).<sup>82-85</sup> Hematopoietic cell transplantation (HCT) is a common procedure among individuals with hematologic malignancies and has been associated with increased VTE risk, principally due to catheter usage.<sup>86</sup> The association between CVADs and VTE may be the result of venous stasis and vessel injury after insertion of the CVAD<sup>87,88</sup> or related to infections as a result of catheter placement.<sup>89,90</sup> One study identified more than one insertion attempt and previous CVAD insertion as significant risk factors for CVAD-related thrombosis, supporting the hypothesis that vessel wall trauma or endothelial damage may contribute to this phenomenon.<sup>85</sup>

Many agents used in cancer treatment are also associated with an increased risk of developing VTE, notably systemic therapy (eg, chemotherapy, protein kinase inhibitors, immunotherapy), hormone therapy with estrogenic compounds, and antiangiogenic agents. The association of systemic therapy with VTE in patients with cancer has been shown in several studies.<sup>2,27,83,91,92</sup> In one population-based case-control study, the ORs for development of VTE were 6.5 and 4.1 for patients with cancer receiving chemotherapy and those not receiving chemotherapy, respectively.<sup>83</sup> It was estimated that the annual incidence of VTE could be as high as 15% in patients with colorectal cancer treated with chemotherapeutic regimens.<sup>92</sup> There is also evidence that pre-chemotherapy thrombocytosis,<sup>27,44,91</sup> leukocytosis,<sup>27</sup> and hemoglobin level <10 g/dL<sup>27,91</sup> are predictive of VTE in patients receiving chemotherapy, although the association of anemia with VTE may be complicated by the use of erythropoiesis-stimulating agents (ESAs).

Exogenous hormonal compounds, such as selective estrogen receptor modulators (eg, tamoxifen, raloxifene for breast cancer), can lead to increased VTE risk.<sup>93-97</sup> Diethylstilbestrol phosphate used in combination with doxorubicin for the treatment of hormone-refractory prostate cancer was reported to increase VTE risk compared with doxorubicin alone.<sup>98</sup> Use of hormonal compounds, such as hormone replacement therapy<sup>99,100</sup> or hormonal contraceptive agents,<sup>101-103</sup> have also been associated with increased risk of developing VTE. VTE risks may vary between different formulations of combined oral contraceptives, depending on the type of progestogen used.<sup>102,104,105</sup> Additionally, progestin-only contraceptives do not definitively increase the risk of VTE in the general population, but may contribute to VTE risk in patients with multiple risk factors.<sup>106</sup>

Finally, the association between immunomodulating agents with antiangiogenic properties (eg, thalidomide in combination with doxorubicin and/or dexamethasone; lenalidomide in combination with dexamethasone) and increased incidence of VTE has been supported by multiple studies, most often in the context of treatment for multiple myeloma. For guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma, available at [www.NCCN.org](http://www.NCCN.org).<sup>107-109</sup> ESAs, which are used to treat anemia in patients with cancer, have also been associated with the development of VTE, and though they remain a reasonable option for supportive care, attention to the safety and risks/benefits must be considered.<sup>3,91,110,111</sup>

### Risk Assessment in Outpatients with Cancer

A predictive model for chemotherapy-associated VTE was published by Khorana et al and has been reproduced and adapted in the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease as a risk assessment tool for outpatients with cancer (see *VTE Risk Assessment in Outpatients with Cancer* in the algorithm).<sup>27</sup> The association of VTE with five readily available clinical and laboratory



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variables (very-high-risk and high-risk cancers associated with an increased risk of VTE, pre-chemotherapy platelet count  $\geq 350 \times 10^9/L$ , hemoglobin  $< 10$  g/dL or use of red cell growth factors, pre-chemotherapy white blood cell count  $\geq 11 \times 10^9/L$ , and BMI  $\geq 35$  kg/m<sup>2</sup>) was characterized in a derivation cohort of 2701 outpatients with cancer from a prospective observational study. A risk model was derived and validated in an independent cohort of 1365 patients from the same study. This risk assessment model (RAM) was externally validated by several retrospective and prospective studies; however, reported rates for developing VTE based on the three risk categories vary widely because of differences in patient populations and follow-up periods.<sup>112-116</sup> In the original study, the rate of symptomatic VTE in the derivation cohort was 0.8%, 1.8%, and 7.1% for the low-, intermediate-, and high-risk categories, respectively. In the validation cohort, the rates were 0.3%, 2%, and 6.7%, respectively.<sup>27</sup> An analysis of 1412 patients from phase I studies with a comparable duration of follow-up reported rates of 1.5%, 4.8%, and 12.9%, respectively, for each of the risk categories. This study also identified the risk assessment score to be the only predictor of VTE.<sup>113</sup> These rates are thus summarized and reported as part of the risk assessment tool for outpatients with cancer (see *VTE Risk Assessment in Outpatients with Cancer* in the algorithm).

The RAM by Khorana et al was also validated and extended by Ay and colleagues,<sup>112</sup> who identified D-dimer and P-selectin as additional discriminatory risk factors for VTE in ambulatory patients with cancer. However, these laboratory tests are not routinely measured in patients with cancer, so their inclusion in routine thrombotic risk assessment should be predicated upon their validation in future studies. In addition to the Vienna CATS RAM,<sup>117</sup> several other RAMs have been published, including the Protecht model,<sup>118</sup> CONKO score,<sup>119</sup> ONKOTEV score,<sup>120</sup> TiC-Onco score,<sup>121</sup> and COMPASS-CAT model.<sup>122</sup> A prospective multicenter study of the Khorana score, the Vienna CATS score, the Protecht score,

and the CONKO score found that the discriminatory performance of these models was modest (C-statistics from 0.50–0.57).<sup>123</sup> This study has been criticized because only 25% (230 of 876) of participants were enrolled at the start of chemotherapy, the highest risk period for VTE. Thus far, only the Khorana risk score has been successfully used in prospective randomized trials of thromboprophylaxis to identify patients at risk.<sup>124,125</sup>

### VTE Prophylaxis in Patients with Cancer

Clinical practice guidelines and data from numerous clinical trials have confirmed that the appropriate use of VTE prophylaxis is safe and effective.<sup>126-130</sup> Despite this, practice survey results indicate that VTE prophylaxis is perhaps still underutilized. The Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey noted that only 50% of surgical oncologists and 5% of medical oncologists routinely used VTE prophylaxis in patients with cancer.<sup>131</sup> Similar results were documented in the multinational IMPROVE and ENDORSE registries of patients hospitalized with medical illness, in which only 45% of patients with cancer received any form of VTE prophylaxis.<sup>132,133</sup> The NCCN Panel recommends identification of patients at risk for developing VTE and subsequent initiation of VTE prophylaxis based on inpatient/outpatient and medical/surgical oncology status.

The Panel does not recommend VTE prophylaxis to prevent CVAD-associated thrombosis in patients with cancer, as in several studies thromboprophylaxis has not been demonstrated to be effective.<sup>134-137</sup> However, a recent systematic review and meta-analysis of 12 randomized controlled trials evaluated the efficacy and safety of thromboprophylaxis in patients with cancer and a CVAD and found that VTE rates were significantly lower in patients receiving thromboprophylaxis compared to those not receiving thromboprophylaxis (7.6% vs. 13%;  $P < .01$ ).<sup>138</sup> Additionally, rates of major bleeding were similar between the two arms (0.9% vs. 0.6%;  $P = .87$ ).<sup>138</sup> In a recent subgroup analysis of the AVERT



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trial, the safety and efficacy of apixaban versus placebo as thromboprophylaxis in 217 patients with cancer and a CVAD was assessed.<sup>139</sup> Rates of VTE were significantly lower in the apixaban arm (4.8% vs. 18.7%;  $P < .0001$ ) and rates of major bleeding events were similar between the two groups, at 1.6% in the apixaban group versus 2.2% in the placebo group ( $P = .556$ ).<sup>139</sup> These data suggest that thromboprophylaxis in patients with cancer and a CVAD may be safe and effective, though future studies are needed to corroborate these findings.

### Inpatient VTE Prophylaxis

#### Population At Risk

Patients with cancer who are hospitalized are at high risk for VTE.<sup>6</sup> The NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease recommend VTE prophylaxis for all adult medical and surgical inpatients with a diagnosis of cancer, excluding those with basal/squamous cell skin cancer. Although multiple RAMs have been developed for patients hospitalized for medical and surgical care,<sup>140-143</sup> none have been validated in prospective management studies for patients with cancer who are hospitalized. Therefore, providers are encouraged to assess VTE risk factors, risks, and benefits of VTE prophylaxis, and to stress the importance of adherence to prevention programs prior to the initiation of VTE prophylaxis.

Adult patients with cancer who are hospitalized should undergo the following evaluation prior to the initiation of thromboprophylaxis: comprehensive medical history and physical examination (H&P), complete blood count (CBC) with platelet count and differential, prothrombin time (PT), activated partial thromboplastin time (aPTT), and comprehensive metabolic panel (CMP) including liver and kidney function tests. In addition to these components, initial workup for inpatient VTE prophylaxis should also include a VTE and bleeding risk assessment.

#### Initial Prophylaxis

If there is no contraindication to anticoagulation (see *Contraindications to VTE Prophylaxis* in the algorithm), prophylactic anticoagulation therapy is recommended (category 1). The recommendation assumes that ambulation in hospitalized patients with cancer is inadequate to reduce VTE risk. Preoperative dosing with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for high-risk surgery (eg, abdominal/pelvic surgery) can be considered with or without an intermittent pneumatic compression (IPC) device.

#### Medical Oncology Inpatients

Anticoagulant options for VTE prophylaxis for patients hospitalized for medical oncology care are LMWHs (dalteparin<sup>144-146</sup> and enoxaparin<sup>147-150</sup>), fondaparinux<sup>151-153</sup> (all category 1 for standard dosing), and UFH<sup>152,154</sup> (category 2A for standard dosing). LMWHs (enoxaparin and dalteparin) are preferred over UFH unless contraindicated (eg, poor renal function). Recommendations are derived from patients with and without cancer hospitalized with a medical illness, most commonly CHF and acute or chronic respiratory disease, who undergo hospitalization for >6 days, have immobility or are on bed rest for ≥3 days, are ≥40 years of age, and have additional risk factors for VTE.<sup>155</sup> The Panel recommends that thromboprophylaxis is carried out for the duration of the hospital stay, for 6 to 14 days, or until the patient is fully ambulatory. A meta-analysis of nine randomized trials concluded that during anticoagulant prophylaxis with LMWHs, fondaparinux, or UFH, patients had significant reductions in any pulmonary embolism (PE) (relative risk [RR], 0.43; 95% CI, 0.26–0.71; absolute risk reduction, 0.29%) and fatal PE (RR, 0.38; 95% CI, 0.21–0.69; absolute risk reduction, 0.25%) compared with no treatment.<sup>155</sup>

Patients hospitalized for medical oncology care can continue apixaban/rivaroxaban prophylaxis if either option is already being used in the outpatient setting; however, apixaban/rivaroxaban should not be

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initiated in the hospital. Apixaban/rivaroxaban prophylaxis is also an option for patients with a history of heparin-induced thrombocytopenia (HIT), for whom a heparin-based regimen is not feasible.

The PREVENT trial demonstrated that fixed-dose dalteparin (5000 units daily) reduced the incidence of VTE in patients with acute medical illness from 4.96% in the placebo group to 2.77% in the dalteparin group (RR, 0.55; 95% CI, 0.38–0.80;  $P = .0015$ ).<sup>146</sup> A subgroup analysis of the PREVENT trial found that dalteparin reduced the incidence of symptomatic VTE, fatal PE, sudden death, or asymptomatic proximal DVT in patients with obesity (2.8% vs. 4.3% with placebo; RR, 0.64; 95% CI, 0.32–1.28) and patients  $\geq 75$  years of age (4.2% vs. 8.0% with placebo; RR, 0.52; 95% CI, 0.31–0.87).<sup>145</sup> In the MEDENOX trial, enoxaparin 40 mg daily led to a significantly lower rate of VTE than placebo (5.5% vs. 14.9%; RR, 0.37; 97.6% CI, 0.22–0.63;  $P < .001$ ) in patients with acute medical illness. In this study, a lower dose of enoxaparin (20 mg daily) did not have the same benefits.<sup>148</sup> Enoxaparin 40 mg daily was explored in two other studies among patients hospitalized with general medical illness and among patients with acute medical illness, respectively, and did not result in a reduction in death rate over placebo.<sup>149,150</sup>

The ARTEMIS trial demonstrated that fondaparinux 2.5 mg daily led to a significantly lower VTE rate compared with placebo among inpatients  $\geq 60$  years of age with acute medical illness (5.6% vs. 10.5%; RR reduction, 46.7%; 95% CI, 7.7%–69.3%).<sup>153</sup> In a randomized trial among patients with heart failure and/or chest infection, UFH 5000 units every 8 hours significantly lowered the frequency of DVT in the legs (26% vs. 4% with placebo;  $P < .01$ ).<sup>154</sup> Multiple studies have shown that dosing UFH 3 times per day is more effective than twice daily in preventing DVT in general surgery and medical inpatients.<sup>126,156,157</sup>

### *Surgical Oncology Inpatients*

It is well-established that low-dose heparin offers an effective way of preventing VTE and VTE-related deaths in the general population undergoing surgery, which also applies to patients with cancer.<sup>126,128,158,159</sup> Anticoagulant options for VTE prophylaxis for patients hospitalized for surgical oncology care are LMWHs (dalteparin,<sup>144,160</sup> enoxaparin<sup>147,161</sup>), fondaparinux,<sup>130,151,162</sup> UFH,<sup>163-166</sup> apixaban<sup>167</sup> (only for patients with gynecologic cancers), and rivaroxaban<sup>168</sup> (only for patients following laparoscopic surgery for colorectal cancer). Recommended doses are derived from studies of patients undergoing planned, elective, open abdominal, or pelvic surgery for malignancy (operating room [OR] time  $> 45$  minutes, patients aged  $> 40$  years). Thromboprophylaxis should be carried out for at least 7 to 10 days or until the patient is fully ambulatory. It must be noted that UFH led to higher rates of HIT in patients hospitalized for surgical care as much as 10-fold compared to LMWHs like enoxaparin.<sup>169</sup>

The recommended prophylactic options are presumed to be equivalent, as studies have not clearly identified a particular anticoagulant regimen to have superior efficacy for the prevention of VTE in patients with cancer.<sup>129,130,166,167,170,171</sup> These comparisons have been made in patients undergoing major abdominal surgery receiving postoperative fondaparinux versus perioperative dalteparin,<sup>130</sup> first-generation LMWH versus UFH,<sup>163,164</sup> enoxaparin versus UFH,<sup>165,166</sup> dalteparin versus UFH,<sup>171</sup> and enoxaparin versus apixaban.<sup>167</sup> In particular, some of these studies focused exclusively on patients undergoing major surgeries for various malignancies, including gynecologic neoplasms and colorectal cancer.<sup>166-168,171</sup> In particular, apixaban prophylaxis should only apply to patients with gynecologic cancers, as data for safety and efficacy are currently only available for this specific population. In the supportive study, apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed and continued for 28 days.<sup>167</sup> Similarly, rivaroxaban prophylaxis



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should only be applied to patients following laparoscopic surgery for colorectal cancer, as data for safety and efficacy are currently only available for this specific population.<sup>168</sup> In the supportive study, patients who had undergone laparoscopic surgery for colorectal cancer received LMWH prophylaxis prior to a switch to rivaroxaban 10 mg daily starting 5 to 9 days following surgery and continued for a total of 3 weeks. It should be noted that the Panel prefers LMWHs (enoxaparin and dalteparin) over UFH unless they are contraindicated.

### *Renal Dosing*

The doses for some anticoagulants might need to be adjusted in both patients hospitalized for medical oncology and surgical oncology care with renal disease. LMWHs are excreted via the kidney; due to pharmacologic and pharmacokinetic differences, there might be variation in the degree of accumulation of various LMWHs in patients with renal impairment.<sup>172</sup> In the TIMI-11A trial in patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS), patients with renal impairment showed a reduction in enoxaparin clearance compared to those with normal renal function.<sup>173</sup> Other studies have supported this observation, noting that the inverse relationship between creatinine clearance (CrCl) and anti-Xa concentrations might be enoxaparin dose-dependent.<sup>174,175</sup> In contrast, dalteparin might not accumulate in patients with severe renal function.<sup>176,177</sup> LMWH accumulation can increase the risk of major bleeding; thus, its benefits must be carefully weighed against potential complications in this subset of patients.<sup>178</sup>

It has been suggested that a reduced dose of enoxaparin in patients with severe renal impairment led to fewer major bleeding events compared with standard doses.<sup>178</sup> Some studies, primarily in the setting of NSTEMI-ACS, comparing the efficacy and safety of enoxaparin versus UFH or enoxaparin versus fondaparinux have found no clinically meaningful difference between these options in patients with renal impairment.<sup>179-182</sup>

The Panel recommends that in patients with severe renal disease (estimated CrCl <30 mL/min), dalteparin, fondaparinux, and rivaroxaban should be avoided, apixaban should be cautioned as limited data exist for its use in this population, and UFH should be used instead.<sup>172</sup> If enoxaparin is used in patients with estimated CrCl <30 mL/min, it should be dosed at 30 mg subcutaneously (SC) once daily.<sup>172</sup> In those with moderate renal disease (CrCl 30–49 mL/min), fondaparinux should be used with caution.<sup>151,152</sup>

### *Dosing for Body Mass Index $\geq 40$ kg/m<sup>2</sup>*

It has been suggested that fixed doses of anticoagulants might not be sufficient in patients with obesity.<sup>183-185</sup> Due to an inverse correlation between anti-Xa levels and body weight, patients with body weight extremes may not achieve adequate anti-Xa levels for maximal anticoagulant effectiveness.<sup>186,187</sup> Although there are limited to no data available to support dosing recommendations for patients with cancer and a BMI  $\geq 40$  kg/m<sup>2</sup>, the NCCN Panel suggests consideration of increased prophylactic anticoagulation doses in patients hospitalized for medical and surgical oncology care in this weight range. The studies supporting these recommended dosing regimens have been carried out in non-oncology populations, primarily in patients undergoing gastric bypass surgery receiving prophylactic dalteparin (7500 units daily,<sup>188,189</sup> 5000 units every 12 hours,<sup>190</sup> or 40–75 units/kg daily<sup>191</sup>), enoxaparin (40 mg every 12 hours<sup>183-185,192-199</sup> or 0.5 mg/kg actual body weight daily<sup>200-204</sup>), fondaparinux (5 mg daily<sup>205</sup>), and UFH (7500 units every 8 hours<sup>196</sup>). Prospective investigations of these dosing regimens are warranted to further ascertain their efficacy for patients with obesity and cancer.

### *Dosing for Actual Body Weight 25–50 kg*

Available data suggest administration of standard VTE prophylaxis doses to patients weighing 25 to 50 kg may result in overexposure and increased bleeding, but there are very limited data available to inform dose reduction



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strategies.<sup>206, 207</sup> Although there are limited data to support dosing recommendations for patients weighing 25 to 50 kg, the NCCN Panel suggests consideration of lower prophylactic doses in patients in this weight range hospitalized for medical or surgical oncology care. For dalteparin, the NCCN Panel suggests lowering prophylactic dose to 2500 units daily or 100 units/kg daily.<sup>208,209</sup> For enoxaparin, the NCCN Panel suggests lowering prophylactic dose to 30 mg daily for patients with an actual body weight of 41 to 50 kg and considering further reduction to 20 mg daily for patients weighing 25 to 40 kg.<sup>207,208</sup> For either weight range, use of enoxaparin should be avoided if CrCl is <30 mL/min. For prophylactic use of enoxaparin in patients weighing 25 to 50 kg, the NCCN Panel recommends the consideration of laboratory monitoring.<sup>210</sup> If dose escalation or de-escalation is required twice, consultation with hematology or a clinical anticoagulation pharmacy specialist is recommended.<sup>210</sup> Use of fondaparinux is contraindicated in those weighing <50 kg.<sup>151</sup> For UFH, the NCCN Panel suggests a prophylactic dose of 2500 units every 8 to 12 hours for those weighing <50 kg.<sup>206</sup> Laboratory monitoring should also be considered in patients using UFH along with consultation with hematology or a clinical anticoagulation pharmacy specialist if dose escalation or de-escalation is required twice.<sup>210</sup>

### **Mechanical Prophylaxis**

In case of contraindication to anticoagulation, mechanical prophylaxis is recommended (for contraindications to mechanical prophylaxis, see *Contraindications to VTE Prophylaxis* in the algorithm). Most data regarding the use of mechanical prophylaxis come from studies of patients hospitalized with surgical needs or stroke and have been extrapolated to the medical population.<sup>211-213</sup> According to one study, no difference was seen in the VTE rate in patients undergoing gynecologic oncology surgery receiving either low-dose heparin or IPC of the calf, even though the former was more frequently associated with postoperative bleeding complications.<sup>211</sup> Additionally, in contrast to graduated compression

stockings (GCS), IPC significantly reduced DVT and was associated with a lower risk of skin complications.<sup>213,214</sup> However, IPC might not be an equivalent substitute for anticoagulants in all scenarios. Results from a retrospective study of patients who had undergone abdominal surgery for gynecologic cancers and received IPC showed that the incidence of PE in patients with cancer (4.1%) exceeded by 14-fold that in patients with benign disease (0.3%).<sup>215</sup> Additionally, results from a randomized trial (including a limited number of patients with cancer) suggest that addition of mechanical prophylaxis to pharmacologic prophylaxis in patients with critical illness may not reduce the incidence of DVT.<sup>216</sup> Other disadvantages of IPC include the potential for interference with ambulation and the need to keep the devices in place nearly continuously until patients are fully ambulatory.

GCS is an alternative mechanical prophylactic method that might provide benefit in VTE reduction, especially when combined with other therapies.<sup>217</sup> However, similar to IPC, it should not be relied upon as the sole method of VTE prophylaxis. First, many studies demonstrating its efficacy were conducted more than a decade ago and used fibrinogen uptake scans as a primary outcome measure—a now antiquated diagnostic method.<sup>218</sup> Additionally, a randomized controlled trial in patients undergoing hip surgery found that GCS did not provide significant additive protection against VTE in patients receiving fondaparinux.<sup>219</sup> Similarly, results from the CLOTS1 trial in patients with stroke found that GCS did not reduce the incidence of DVT and was associated with a 4-fold increase in the frequency of skin ulcers and necrosis.<sup>214</sup> In addition, the GAPS study noted that pharmacologic VTE prophylaxis was non-inferior to pharmacologic prophylaxis combined with GCS; therefore, GCS may be unnecessary in patients undergoing surgery who are receiving pharmacologic thromboprophylaxis.<sup>220</sup> Most of these trials either did not include patients with cancer or only included a small number of patients



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with cancer. Thus, IPC or GCS should only be used when prophylactic anticoagulants are contraindicated.

Overall, clinicians should discuss VTE prevention and the risks/benefits of pharmacologic and mechanical VTE prophylaxis with patients. Institutions are strongly encouraged to implement best practice programs to monitor provider and patient adherence to VTE prophylaxis.

### VTE Prophylaxis Following Discharge and for At-Risk Ambulatory Patients with Cancer

#### Population At Risk

Certain groups of patients with cancer are known to remain at risk for VTE after discharge from the hospital. In a systematic review of VTE, 74% of patients were diagnosed in the outpatient setting, with a substantial portion having undergone surgery (23%) or hospitalization (37%) in the preceding 3 months.<sup>221</sup> Furthermore, in the @RISTOS observational cohort study of patients undergoing general, urologic, and gynecologic cancer surgeries, 40% of VTE events occurred later than 21 days postoperatively and greatly exceeded hemorrhagic complications as a cause of death.<sup>13</sup> The NCCN Panel identifies patients at risk for VTE to be adults with a diagnosis of cancer hospitalized for medical or surgical care, patients who received VTE prophylaxis during hospitalization, inpatients with cancer intended for discharge, and any outpatients at risk based on VTE risk assessment. Providers are encouraged to assess VTE risk factors, bleeding risk factors, and risks and benefits of VTE prophylaxis, and to stress the importance of adherence to prevention programs and patient preference prior to the initiation of VTE prophylaxis.

#### Prophylaxis

##### Medical Oncology Patients

Although there is a lack of consistent evidence to support extended outpatient prophylaxis in most populations of ambulatory patients with

cancer, it is recommended for patients with multiple myeloma receiving highly thrombogenic regimens. For guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma, available at [www.NCCN.org](http://www.NCCN.org).

The Khorana risk score can be used to assess VTE risk in other patients receiving medical oncology care in the outpatient setting (excluding those with multiple myeloma, acute leukemia, myeloproliferative neoplasms, and primary/metastatic brain tumors) receiving/starting systemic therapy for their cancer (see *VTE Risk Assessment in Outpatients with Cancer* in the algorithm). Patients receiving hormonal therapy were excluded from the AVERT trial, but not the CASSINI trial; therefore, they should still be evaluated for VTE risk. Those with low risk for VTE (Khorana score <2) do not need routine VTE prophylaxis. Those with an intermediate or high risk of VTE (Khorana score ≥2) should consider anticoagulant prophylaxis for up to 6 months or longer, if risk persists. Anticoagulant options for VTE prophylaxis for ambulatory patients with cancer include direct oral anticoagulants (DOACs) (apixaban<sup>125</sup> and rivaroxaban<sup>124</sup>) and LMWHs (dalteparin<sup>222</sup> and enoxaparin<sup>223</sup>). The recommended dosing is derived from clinical trials of ambulatory patients with cancer at high thrombotic risk (>18 years of age, Khorana risk score for VTE >2, initiating a new course of chemotherapy) and are not included in product labeling. DOACs are primarily absorbed in the stomach, proximal small bowel (apixaban and rivaroxaban), and colon (apixaban only). Therefore, patients who have had significant resections of these portions of the intestinal tracts may be at risk for suboptimal absorption. See *Therapeutic Anticoagulation for VTE: DOACs: GI Considerations and Alternative Routes of Administration* in the algorithm. Importantly, patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with DOACs.

DOACs have demonstrated efficacy in preventing VTE in ambulatory patients with cancer.<sup>124,125</sup> Specifically, the rate of VTE significantly

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decreased with apixaban prophylaxis versus placebo (4.2% vs. 10.2%; hazard ratio [HR], 0.41; 95% CI, 0.26–0.65;  $P < .001$ ).<sup>125</sup> Furthermore, rivaroxaban prophylaxis yielded a lower incidence of VTE compared to placebo (6.0% vs. 8.8%; HR, 0.66; 95% CI, 0.40–1.09;  $P = .10$ ).<sup>124</sup> It is recommended that LMWHs be considered in patients with advanced unresectable or metastatic pancreatic cancer. In particular, dalteparin has been shown in this group of patients to significantly reduce the incidence of VTE from 23% to 3.4% ( $P = .002$ ).<sup>222</sup> The CONKO-004 trial also reported a significantly decreased rate of symptomatic VTEs in patients with pancreatic cancer in the enoxaparin group versus the observation group (6.4% vs. 15.1%; HR, 0.40; 95% CI, 0.19–0.83;  $P = .01$ ).<sup>223</sup>

### *Surgical Oncology Patients*

The Panel recommends prophylaxis for up to 4 weeks postoperatively for patients who have undergone high-risk abdominal or pelvic cancer surgery.<sup>13,215</sup> These include patients undergoing surgery for gastrointestinal (GI) malignancies, those with a previous episode of VTE, anesthesia time  $>2$  hours, perioperative bed rest for  $\geq 4$  days, advanced-stage disease, and age  $>60$  years.<sup>13</sup> Extended anticoagulant options for patients hospitalized for surgical oncology care are listed within *VTE Prophylaxis* in the algorithm. DOACs (apixaban<sup>167</sup> and rivaroxaban<sup>168</sup>) and LMWHs (dalteparin<sup>160,223,224</sup> and enoxaparin<sup>161,167,224</sup>) are recommended options for this group of patients. The recommended dosing is derived from studies of patients undergoing planned, elective, open abdominal, and pelvic surgery for malignancy (OR time  $>45$  minutes, patients aged  $\geq 40$  years).

Multiple studies have demonstrated the clinical benefit of extended VTE prophylaxis for patients undergoing major surgeries.<sup>160,161</sup> In a study evaluating the optimal duration of dalteparin in patients after major abdominal surgery, the cumulative incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis (7-day) to 7.3% with prolonged thromboprophylaxis (28-day) (RR reduction, 55%; 95% CI, 15–76;  $P =$

.012).<sup>160</sup> Another study in patients after abdominal or pelvic surgery for cancer showed that the rates of VTE were 12.0% in the placebo group and 4.8% in the enoxaparin group ( $P = .02$ ) at 4 weeks, a significant difference that persisted at 3 months (13.8% vs. 5.5%;  $P = .01$ ).<sup>161</sup> Data from a meta-analysis comparing prolonged thromboprophylaxis with LMWH versus control showed that the incidence of overall VTE after major abdominal or pelvic surgery was reduced from 13.2% in the control group to 5.3% in patients receiving out-of-hospital LMWH (Mantel-Haentzel [MH] OR, 0.38; 95% CI, 0.26–0.54).<sup>225</sup>

As previously discussed, apixaban<sup>167</sup> and rivaroxaban<sup>168</sup> prophylaxis should only be applied to patients with gynecologic cancers and patients following laparoscopic surgery for colorectal cancer, respectively, as data for safety and efficacy are currently only available for these specific populations.

### *Renal Dosing*

The rationale and guidance for anticoagulant usage in patients with renal disease is the same for patients with cancer who are receiving treatment while hospitalized or in an outpatient setting. Apixaban should be cautioned in patients with CrCl  $<30$  mL/min due to limited data in this population, but may be considered in extenuating circumstances, such as HIT. Rivaroxaban, as well as dalteparin and enoxaparin, should be avoided in patients with a CrCl  $<30$  mL/min.<sup>124,125</sup>

### *Other Dose Modifications for Ambulatory Patients and Patients Post-Discharge at Risk for VTE*

In order to balance bleeding risk and VTE likelihood, the NCCN Panel recommends that prophylactic anticoagulation therapy be avoided in patients hospitalized for medical oncology care whose platelet counts are  $<50,000/\mu\text{L}$ . The NCCN Panel also recommends avoiding the use of prophylactic apixaban in patients hospitalized for medical oncology care



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weighing <40 kg (see *Contraindications to VTE Prophylaxis* in the algorithm).

### Contraindications to VTE Prophylaxis

#### Contraindications to Prophylactic Anticoagulation

Contraindications to anticoagulation can be relative or absolute, and temporary or permanent. Consideration of the degree of contraindication to anticoagulation and its duration are essential when evaluating the risks and benefits of anticoagulation (see *Contraindications to VTE Prophylaxis* in the algorithm).

It must be noted that patients with a recent history of bleeding associated with the central nervous system or a spinal lesion are at increased risk of anticoagulant-associated bleeding. Package inserts for LMWHs and fondaparinux include boxed warnings specifying that the risk for spinal or epidural hematoma resulting in long-term paralysis is increased when these anticoagulants are administered to patients receiving epidural or spinal anesthesia or those undergoing spinal puncture.<sup>144,147,151</sup> UFH should also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture.<sup>144,147,151</sup> Anticoagulant prophylaxis is usually considered unsafe for platelet counts <50,000/ $\mu$ L.<sup>226</sup> Data on withholding or lowering doses of anticoagulants in the case of significant thrombocytopenia have been reported mostly for the treatment of VTE in retrospective cohort studies and case series of patients with hematologic malignancies.<sup>227-229</sup>

Of note, a prolonged aPTT is not considered a contraindication to anticoagulation therapy in patients with a lupus inhibitor or lupus anticoagulant, such as those diagnosed with APS. Antiphospholipid antibodies prolong the aPTT by interfering with the interaction between coagulation factors in the patient plasma sample and the phospholipids provided in the aPTT test reagent. Antiphospholipid antibodies have been

associated with an increased risk for venous and arterial thromboembolism and adverse pregnancy outcomes.<sup>230,231</sup> Any patient who has experienced a thrombotic event and fulfills diagnostic criteria for APS should be considered for indefinite anticoagulation therapy.<sup>231</sup>

Specific use of LMWH or UFH for prophylactic anticoagulation is contraindicated in patients with current or previous HIT (see *Heparin-Induced Thrombocytopenia* in the algorithm) as well as for patients with a pork product allergy. For additional agent-specific contraindications, see *Therapeutic Anticoagulation for VTE* in the algorithm.

#### Contraindications to Mechanical Prophylaxis

Whenever mechanical prophylaxis is employed, steps should be taken to ensure its proper use and continuous application (see *Contraindications to VTE Prophylaxis* in the algorithm). Mechanical prophylaxis should not be used in patients with an acute DVT unless they are on therapeutic anticoagulation. In addition, consideration of risks and benefits should be weighed in the presence of large hematomas. It has been established earlier that skin ulceration or wounds might be a particular concern for GCS, as opposed to IPC.<sup>213,214</sup> Other contraindications for GCS include arterial insufficiency and peripheral neuropathy (due to potential skin damage). In particular, it has been shown that the use of GCS on legs with impaired arterial flow can worsen ischemia.<sup>232</sup>

### Evaluation and Treatment of VTE in Patients with Cancer

#### Evaluation and Treatment of Acute Superficial Vein Thrombosis

Even though few data are available on the incidence of acute superficial vein thrombosis (SVT) in patients with cancer, it has been estimated that the majority of SVT occur in the lower extremities (most often in the great saphenous vein) and external jugular veins.<sup>233,234</sup> SVT is more likely than DVT to be symptomatic, especially if occurring in the lower extremities.

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Intravenous (IV) catheter or peripherally inserted central catheter (PICC)-related SVT, sometimes referred to as infusion thrombophlebitis, is often associated with a palpable tender cord along the course of the affected vein. PICC-related SVT has been estimated to occur in 29% of patients who are hospitalized requiring IV therapy for >5 days.<sup>235</sup>

Although SVT does not generally have the same implications for morbidity and mortality as DVT, the OPTIMEV study in patients with cancer reported that patients with isolated SVT had similar risks of death and DVT/PE recurrence to patients with DVT. These risks were higher than those in patients with SVT without cancer.<sup>236</sup> Furthermore, SVT and DVT can occur simultaneously and each predisposes the patient to the other condition.<sup>233,236,237</sup> In a retrospective cohort study to determine the risk of arterial and venous complications after a spontaneous SVT in the leg, DVT was reported as the only primary outcome to show a significant relationship with SVT (OR, 10.2; 95% CI, 2.0–51.6).<sup>238</sup> An extensive SVT in the saphenous vein can progress to involve the deep venous system at the saphenofemoral junction.<sup>239–241</sup> Such clots can precipitate PE.<sup>240</sup> An observational study of patients with symptomatic SVT reported that approximately 10% of patients developed thromboembolic complications at 3-month follow-up (DVT, PE, extension or recurrence of SVT) despite anticoagulation use in about 90% of individuals.<sup>233</sup> In particular, male sex, active solid cancer, personal history of VTE, and saphenofemoral involvement have been reported among the factors significantly associated with concurrent or future DVT/PE in patients with SVT.<sup>237,242,243</sup> In one study, the prevalence of malignancy was reported to be 18.8% among patients with SVT and concurrent DVT/PE, compared with 4.2% among those with isolated SVT ( $P < .001$ ).<sup>237</sup>

### Evaluation

Diagnosis of SVT is made primarily on the basis of clinical symptoms, which consist of pain, erythema, and tenderness involving a superficial

vein in the extremity. Workup consists of comprehensive H&P, CBC with platelet count, PT, aPTT, liver and kidney function tests, as well as venous ultrasound (US) based on clinical judgment, especially if the possibility of proximal deep vein involvement exists. Progression of symptoms should be accompanied by follow-up imaging.

### Treatment

For SVT involving the upper extremity (median, basilic, and/or cephalic veins), if a peripheral catheter is involved and is no longer indicated, the first step is to remove the catheter. For patients with SVT associated with a PICC line, catheter removal may not be necessary, especially if the patient is treated with anticoagulation and/or if symptoms resolve. Whether or not a catheter is involved, symptomatic treatment involving warm compresses, nonsteroidal anti-inflammatory drugs (NSAIDs), and elevation of the affected limb should be used as clinically indicated. Aspirin and NSAIDs should be avoided in patients with platelet counts <20,000 to 50,000/mcL or with severe platelet dysfunction. If there is symptomatic progression or progression on imaging, prophylactic dose anticoagulation is recommended. Anticoagulation at prophylactic doses, such as rivaroxaban 10 mg PO daily and fondaparinux 2.5 mg SC daily for 45 days, has been shown to be effective in some studies that included a limited number of patients with cancer.<sup>244–246</sup> Specifically, in a small randomized trial, rivaroxaban was determined to be effective and safe in the treatment of SVT in the legs when compared with placebo based on parameters such as treatment “failure” (defined in the study as requirement for an alternative, non-study anticoagulant); development of proximal DVT or PE; or requirement for surgery for SVT (1 vs. 5 patients; absolute risk reduction 9.0%; 95% CI, -22% to 5.9%) and leg pain improvement ( $P = .011$ ) by 90 days.<sup>245</sup> In the much larger CALISTO trial, fondaparinux resulted in significantly reduced composite of death from any cause, symptomatic DVT/PE, symptomatic extension to the saphenofemoral junction, or symptomatic recurrence of SVT over placebo

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(0.9% vs. 5.9%; RR reduction 85%; 95% CI, 74–92;  $P < .001$ ).<sup>246</sup> In the randomized, phase 3b SURPRISE trial, rivaroxaban was non-inferior to fondaparinux for the treatment of SVT in terms of symptomatic DVT/PE, progression or recurrence of SVT, and all-cause mortality (3% vs. 2%; HR, 1.9; 95% CI, 0.6–6.4;  $P = .0025$ ).<sup>244</sup>

Therapeutic dose anticoagulation should be considered if the clot is in close proximity (defined as within approximately 3 cm) to the deep venous system (see *Therapeutic Anticoagulation for VTE* in the algorithm).

For SVT involving the lower extremity (great and small saphenous veins), prophylactic dose anticoagulation is recommended for at least 6 weeks if SVT is >5 cm in length or if SVT extends above the knee. Therapeutic dose anticoagulation is recommended for at least 3 months if the SVT is within 3 cm of the saphenofemoral junction (see *Therapeutic Anticoagulation for VTE* in the algorithm). Additionally, repeat US should be considered in 7 to 10 days if the SVT is <5 cm in length or below the knee. If progression is indicated on US, prophylactic dose anticoagulation should be considered.

### Evaluation and Treatment of Acute Deep Vein Thrombosis

There have been a limited number of investigations on the long-term sequelae of DVT, especially in patients with cancer. A prospective study in patients with symptomatic DVT showed that the cumulative incidence of recurrent VTE was 17.5% after 2 years of follow-up, 24.6% after 5 years, and 30.3% after 8 years. The cumulative incidence of the post-thrombotic syndrome (PTS), a frequent complication of DVT, was 22.8%, 28.0%, and 29.1% after 2, 5, and 8 years, respectively.<sup>247</sup> Some other studies have examined the prognostic significance of different subtypes of DVT. Data from OPTIMEV and the Cleveland Clinic examining isolated cancer-associated distal DVT and isolated proximal DVT individually came to the conclusion that the two conditions had similar prognoses; however,

cancer-associated isolated distal DVT had dramatically poorer prognosis compared to those without cancer.<sup>248,249</sup> The risk of VTE recurrence for patients with isolated distal DVT was reported in another study to be as high as 15.3% despite anticoagulant therapy in 99% of patients.<sup>250</sup> A prospective, multicenter cohort study of 3032 patients who had venous ports implanted reported the incidence of catheter-related thrombosis with or without PE at 12 months to be 3.8%.<sup>251</sup> Recurrent VTE, bleeding complications, and mortality rates among patients with upper-extremity DVT were reported in a systematic review to average 5.1%, 3.1%, and 24% in prospective studies and 9.8%, 6.7%, and 35% in retrospective studies, respectively.<sup>252</sup> According to data from the RIETE Registry, at presentation, patients with arm DVT often have less clinically overt PE than those with lower-limb DVT (9.0% vs. 29%; OR, 0.24; 95% CI, 0.18–0.33), but their 3-month outcome is similar. Among patients with arm DVT, those with cancer had an increased incidence of major bleeding, recurrent VTE, and death compared to those with catheter-related DVT.<sup>253</sup>

### Evaluation

Classic clinical symptoms are not present in all cases of acute DVT; however, clinical suspicion is warranted in case of swelling of the unilateral extremity; heaviness in the extremity distal to the site of the venous thrombosis; pain in the extremity; unexplained persistent calf cramping; swelling in the face, neck, or supraclavicular space; and catheter dysfunction (if a catheter is present). DVT may also be an incidental finding. The most common presenting symptoms of DVT presented in the MASTER registry were extremity edema, pain, and erythema, which were observed in 80%, 75%, and 26% of patients with DVT, respectively.<sup>254</sup> Diagnosis of DVT in adults with cancer should be tempered by an increased level of clinical suspicion on presentation of any clinically overt signs/symptoms that could represent an acute DVT. For patients for whom there is a high suspicion of DVT that do not have contraindications to



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anticoagulation, early initiation of anticoagulation should be considered while awaiting results from imaging studies.

Workup consists of comprehensive medical H&P, CBC with platelet count, PT, aPTT ± fibrinogen, and liver and kidney function tests. Venous US is the preferred imaging method for the initial diagnosis of DVT and has been shown to detect asymptomatic DVT of the lower extremities in 34% of patients who are non-ambulatory with advanced cancer in a small prospective study.<sup>255</sup> It has been reported that two normal US examinations obtained 1 week apart can be used to exclude progressive lower-extremity DVT.<sup>256</sup>

In cases of negative or indeterminate US results following repeat venous imaging and a continued high clinical suspicion of DVT, other venous imaging modalities are recommended and include repeat venous US, contrast-enhanced CT venography (CTV), and magnetic resonance venogram (MRV) with contrast. CTV has been reported to be as accurate as US, particularly in diagnosing femoropopliteal DVT.<sup>257,258</sup> This method might be superior to US in detecting thrombus in large pelvic veins and the inferior vena cava (IVC).<sup>258</sup> However, this method requires relatively high concentrations of contrast agent. Conversely, MRV with contrast allows enhanced venous signal and was reported in a meta-analysis to have higher sensitivity for proximal DVT than distal DVT, with equivalent sensitivity and specificity to US for diagnosing DVT.<sup>259</sup> Some prospective studies suggested that MRV was more sensitive than US in the detection of lower-extremity DVT,<sup>260</sup> and extension of DVT,<sup>261</sup> and might be a valuable technique for assessing iliofemorocaval venous thrombosis.<sup>262</sup> Drawbacks to this method include higher cost, longer imaging times, and limited availability in some practice settings.<sup>263</sup> Standard invasive venography, once considered the gold standard for DVT diagnosis, has largely been replaced by less invasive methods such as US and MRV, which provide equivalent accuracies.<sup>262-264</sup> Venography remains an

important imaging modality when performed in conjunction with pharmacomechanical thrombectomy/thrombolysis. If all imaging tests are negative for DVT, reassurance should be provided and symptoms should be further evaluated for other causes.

The risk factors for upper-extremity DVT differ from those for lower-extremity DVT, as upper-extremity DVT is frequently related to the presence of a CVAD<sup>82,84,265</sup> and associated with insertion attempts, previous insertion, or catheter placement.<sup>85,266</sup> It must be noted that neither a clot within a catheter nor a simple fibrin sheath around a catheter represents a DVT. Clinical suspicion of catheter-related DVT is warranted when a patient presents with unilateral limb swelling, pain in the supraclavicular space or neck, or catheter dysfunction. Workup for catheter-related DVT consists of venous US, CTV with contrast, MRV with contrast, and x-ray venogram with contrast. Venous US has been reported to accurately detect DVT in the peripheral upper extremity, in the brachial, distal subclavian, and axillary veins. In patients with catheters with isolated flow abnormalities, contrast venography may be preferred.<sup>84,267</sup> Invasive venography for the detection of upper-extremity DVT should be performed through a peripheral vessel in the extremity, although venous access may be limited by edema. If no DVT is identified, symptoms should be evaluated for other causes and further diagnostic imaging/testing should be considered if initial testing is unrevealing or clinical suspicion remains high.

### **Treatment**

#### ***DVT Involving the Proximal Lower Extremity***

For patients with thrombosis in the pelvic and iliac veins, the IVC, and the femoral/popliteal veins, anticoagulation is recommended if no contraindication is present. Catheter-directed therapy (pharmacomechanical thrombolysis or mechanical thrombectomy) can be considered in appropriate candidates. Appropriate candidates for





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catheter-directed therapies include: patients at risk for limb loss (eg, phlegmasia cerulea dolens), patients with central thrombus propagation in spite of anticoagulation, and those with moderate to severely symptomatic proximal DVT. If deemed appropriate for thrombolysis, the choice of regimen for thrombolysis should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues (see *Thrombolytic Agents* and *Contraindications to Thrombolysis and Indications for Thrombolysis* in the algorithm). Compression therapy for symptom control can be considered if therapeutic anticoagulation is tolerated. Since the SOX trial reported that GCS did not reduce the incidence of PTS after a first proximal DVT, routine prescription of GCS after DVT for the purpose of reducing PTS is not recommended.<sup>268</sup> If a contraindication to anticoagulation is present, an IVC filter, preferably retrievable, is recommended, as long as contraindication persists or is likely to recur. Patients should be re-evaluated regularly for change in the status of contraindication to anticoagulation until the contraindication is resolved, at which point anticoagulation should be initiated and IVC filter removed.

### *DVT Involving the Distal Lower Extremity*

For patients with thrombosis in the peroneal, anterior and posterior tibial, and muscular (soleus and gastrocnemius) veins, anticoagulation is recommended unless contraindication is present. If a contraindication is present, follow-up with serial US is recommended. If US indicates progression of DVT to the popliteal vein, treatment should be initiated as outlined previously. Otherwise, local progression (but not to proximal deep vein) can be closely monitored for any change in status, in terms of both progression and contraindication to coagulation. If there is no progression of DVT, the patient should be followed as clinically indicated.

### *DVT Involving the Upper Limb/Chest*

For patients with thrombosis in the brachiocephalic, subclavian, axillary, internal jugular, and brachial veins, and the SVC, anticoagulation and catheter-directed therapy in appropriate candidates should be prescribed with the same caveats as DVT involving the proximal lower extremity. GCS are rarely considered in this setting. In the case of a contraindication to anticoagulation, patients should be followed until contraindication resolves or DVT progression occurs, at which point re-evaluation of the risk/benefit of anticoagulation is recommended (see *Elements for Consideration in Decision Not to Treat* in the algorithm).

### *Catheter-Related DVT*

For patients with catheter-related DVT, in the absence of contraindication, anticoagulation is recommended. Anticoagulation without catheter removal is the preferred option for initial treatment, even for patients with asymptomatic DVT, provided that the catheter is necessary, functional, and free of infection. Catheter removal should be considered otherwise. Anticoagulation is continued for at least 3 months. If the catheter remains in place, then anticoagulation should continue as long as the catheter is present. However, it is important to recognize that there is very little clinical evidence regarding the appropriate duration of anticoagulation for catheter-associated DVT. The recommended duration of therapy also depends on tolerance of anticoagulation, response to anticoagulation, and catheter status. Longer duration of anticoagulation can be considered in patients with catheters with poor flow, persistent symptoms, or unresolved thrombus. Shorter duration of anticoagulation can be considered if the clot or symptoms resolve in response to anticoagulation and/or catheter removal. Catheter-directed thrombolysis (CDT) is rarely considered with the same caveats as DVT involving the proximal lower extremity. In the case of contraindication to anticoagulation, catheter removal is recommended, or the patient should be followed with serial imaging until contraindication is resolved, at which point anticoagulation is

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recommended for at least 3 months. Otherwise, the patient should be re-evaluated for risk/benefit of anticoagulation.

### *Anticoagulation for DVT*

Several studies have supported the use of anticoagulation specifically for the treatment of DVT in the non-cancer population. A meta-analysis comparing UFH and LMWHs found that LMWHs reduced mortality rates over 3 to 6 months of patient follow-up (OR, 0.71; 95% CI, 0.53–0.94;  $P = .02$ ), as well as major bleeding complications (OR, 0.57; 95% CI, 0.33–0.99;  $P = .047$ ), even though the absolute risk reduction was small and not statistically significant (0.61%; 95% CI, -0.04% to 1.26%;  $P = .07$ ).<sup>269</sup> This comparison was also made in a systematic review that compiled five studies enrolling a total of 1636 patients with proximal (above the knee) DVT. A sub-analysis of these trials showed statistically significant reductions favoring LMWH in three areas: thrombotic complications; major hemorrhages; and overall mortality.<sup>270</sup> Data from the Cancer-DACUS study suggest that LMWH for up to 6 months is just as effective as a 12-month course in preventing recurrence for patients with cancer-associated DVT of the lower limbs and subsequent residual vein thrombosis.<sup>271</sup> The NCCN Panel recommends a minimum anticoagulation duration of 3 months. The presence of active cancer, ongoing cancer treatment, an unprovoked DVT, or persistent thrombosis are reasons to consider continuation of anticoagulation. In a systematic review of 11 studies involving 3019 patients with cancer-associated VTE, both rates of VTE recurrence and major bleeding were assessed to investigate the risk/benefit of continuing anticoagulation beyond 6 months.<sup>272</sup> It was noted that VTE recurrence remains common between 6 to 12 months after a cancer-associated VTE, though the risk is lower in this time frame compared to the first 6 months following the event. For example, this study highlights the Hokusai-VTE Cancer study, which revealed a VTE recurrence rate of 7.6% in the first 6 months compared to 2.1% between 6 to 12 months in patients with cancer receiving extended anticoagulant therapy.<sup>272,273</sup> This systematic review also

noted an acceptable safety profile of extended anticoagulation between 6 to 12 months following a cancer-associated VTE, with major bleeding rates between 1% to 4% in patients receiving anticoagulation compared to 0% to 1% in those not receiving anticoagulation.<sup>272</sup>

No randomized controlled trials have reported the effects of particular therapeutic strategies on outcomes of catheter-related DVT. In one prospective study, patients with catheter-related thrombosis received anticoagulants alone, anticoagulants and catheter removal, or no treatment; none had recurrent thrombosis or symptomatic PE.<sup>85</sup> Another study demonstrated that anticoagulation with dalteparin followed by warfarin was not associated with recurrent VTE or line removal due to infusion failure or recurrence/extension of DVT.<sup>157</sup> In the Catheter 2 study, treatment with rivaroxaban for 12 weeks showed preservation of line function at 100% by study endpoint. The risk of recurrent VTE was 1.43%, with one episode of fatal PE.<sup>274</sup> It must be noted that these studies enrolled a small number of patients and thus, their results should be interpreted with care.

The NCCN Panel recommends that the effectiveness of anticoagulation in patients with established DVT be monitored clinically during and after treatment. Follow-up examinations and imaging evaluations allow physicians to detect clot progression in patients undergoing anticoagulation, detect DVT recurrence after successful treatment, and identify chronic injury to the venous system. These studies should be performed in response to symptoms.

### **Evaluation and Treatment of Acute Pulmonary Embolism**

#### ***Evaluation***

Clinical suspicion of PE depends on the presence of current DVT or a recent history of DVT, or presentation of any clinically overt signs or symptoms of PE, including unexplained shortness of breath, chest pain





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(particularly pleuritic chest or back pain), tachycardia, apprehension or tachypnea, syncope, and hypoxemia. In the prospective multicenter MASTER registry, the most common presenting symptoms of PE were dyspnea, pain, and tachypnea, which were present in 85%, 40%, and 29% of patients with PE, respectively.<sup>254</sup> In the International Cooperative Pulmonary Embolism Registry, the most common symptoms at PE diagnosis were dyspnea (82%), chest pain (49%), cough (20%), syncope (14%), and hemoptysis (7%).<sup>275</sup> PE may also be an incidental finding.

Workup consists of a comprehensive medical H&P, CBC with platelet count, PT, aPTT, liver and kidney function tests, N-terminal prohormone B-type natriuretic peptide (NT-proBNP)/troponin evaluation, chest x-ray, and electrocardiogram (ECG). In cases with a high suspicion of PE and no contraindications, early initiation of anticoagulation should be considered while waiting for imaging results. Chest x-rays may not be necessary if a CT angiography (CTA) is planned. It should be noted that repeat imaging and diagnostic studies are not routinely needed in patients with incidental PE and outpatient care should be considered for these patients.

The preferred imaging technique for the initial diagnosis of PE is CTA, which allows for indirect evaluation of pulmonary vessels. Advantages of this method include accurate imaging of mediastinal and parenchymal structures; accurate visualization of emboli in many regions of the pulmonary vasculature; ability to be performed in conjunction with indirect CTV, which can detect DVT<sup>276,277</sup>; and ability to detect signs of right ventricular (RV) enlargement, which can be used in assessing risk for adverse clinical outcomes.<sup>278,279</sup> Disadvantages of CTA include the associated radiation exposure and the need for large amounts of IV contrast, particularly when CTA is followed by indirect CTV.<sup>276</sup>

Alternative imaging modalities used for the diagnosis of PE include: 1) X-ray pulmonary angiography with contrast, which is infrequently used today because of its invasive nature. When used, this method is often

combined with clot extraction or thrombolytic therapy; 2) Magnetic resonance angiography (MRA) with contrast; and 3) Ventilation-perfusion (VQ) scan if CTA is contraindicated (eg, renal insufficiency, contrast allergy refractory to anaphylaxis prophylaxis, and pregnancy, since a VQ scan is associated with less fetal radiation exposure than CTA). In a randomized, single-blind, noninferiority study, VQ scans identified significantly fewer PE than CTA (14.2% vs. 19.2%; 95% CI, 1.1%–8.9%). However, there was no difference in the number of symptomatic VTE that occurred within 3 months in patients in whom PE was considered to be excluded (CTA 0.4% vs. VQ scan 1.0%; 95% CI, 1.6%–0.3%).<sup>280</sup> Patients >70 years of age are more likely than younger patients to be diagnosed with an intermediate-probability VQ scan result.<sup>281</sup> Both intermediate- and low-probability VQ scan results lack diagnostic utility and should be considered indeterminate. In the setting of high clinical suspicion for PE, a high-probability VQ scan is diagnostic.

### *Clinical Prediction Tools for PE*

Even though Wells criteria and D-dimer testing have been shown to be useful in the diagnosis of DVT/PE, with comparable results to conventional radiologic imaging strategies, patients with cancer made up a small number of patients in these studies.<sup>282,283</sup> One study using the Wells criteria and D-dimer testing in the diagnosis of PE noted the performance of this strategy was comparable in patients with and without cancer; however, the number of patients with symptomatic VTE during follow-up was 4-fold higher than that in the total study population (2% vs. 0.5%). In addition, the number needed to test in order to rule out PE in one patient was 3-fold higher in patients with cancer compared to patients without cancer.<sup>284</sup> Results of a large prospective study of patients with suspected DVT in whom DVT had been excluded on radiologic testing showed that high D-dimer levels were present in a large percentage of patients with cancer.<sup>285</sup> Other studies have supported that Wells criteria and D-dimer



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testing were less predictive of PE in patients with cancer.<sup>286-289</sup> Therefore, most patients with cancer undergo imaging to exclude a diagnosis of PE.

The Panel recommends risk stratification for patients with PE.<sup>290,291</sup> Cardiac biomarkers such as troponin, which is released due to endomyocardial damage, and NT-proBNP, as well as cardiac imaging results (ie, RV enlargement on echocardiography, CTA) and the presence of residual DVT on lower-extremity duplex imaging have demonstrated high predictive values for overall mortality in patients with PE.<sup>275,278,292-299</sup> NCCN recommends the use of these tools, together with clinical judgment, in assessing risks in patients with PE. It has been demonstrated that combining the results from at least two of the above tests improved the specificity and positive predictive value compared with the use of individual tests alone in identifying patients at high risk for PE-related mortality.<sup>290</sup> Since the 3-month mortality rate of patients with PE has been reported to be 15%,<sup>275</sup> outpatient care of PE should be limited to individuals at low risk as identified by clinical, laboratory, and imaging assessment.

Clinical risk assessment tools have been developed to assess the advisability of outpatient treatment and intensity of initial follow-up and treatment. Generic scoring systems such as the Pulmonary Embolism Severity Index (PESI),<sup>300,301</sup> the Hestia criteria,<sup>302</sup> and the Geneva Prognostic Score (GPS)<sup>303</sup> are validated tools that can be used to determine risk for an adverse outcome associated with PE. However, it has been suggested that the PESI score might not be useful in patients with cancer.<sup>304</sup> On the other hand, scoring systems such as the Computerized Registry of Patients with Venous Thromboembolism (RIETE), POMPE-C, as well as the EPIPHANY index, predict PE-related mortality risk and have been specifically developed for and externally validated in patients with cancer.<sup>305-309</sup> One study postulated that cancer-specific prognostic scores performed better than generic scales in

estimating PE mortality in patients with cancer.<sup>310</sup> Other comparative studies, however, have not found such an association.<sup>311,312</sup> Therefore, these scores can be included as an adjunct risk assessment tool, but should not be substituted for the above risk-stratification procedures until data from large, prospective trials in patients with cancer are available.

### **Treatment**

Once a diagnosis of PE is made, anticoagulation therapy is recommended for all patients with acute PE who do not have a contraindication to such therapy,<sup>313</sup> including patients with incidental or subsegmental PEs. Anticoagulation should be continued after acute management of PE unless there is extension of VTE or new VTE while on recommended therapy (see *Progression or New Thrombosis on Therapeutic Anticoagulation* in the algorithm). Outpatient care should be considered for PE in patients at low risk with echocardiography or CTA to assess RV overload, NT-proBNP, troponin, and lactate levels also being considered in these patients.<sup>314</sup> After assessment of the cancer status, the physician should consider the use of systemic thrombolysis or CDT or embolectomy for hemodynamically unstable PE.<sup>313,315</sup> Hemodynamically unstable PE is defined as acute PE with sustained hypotension (systolic blood pressure <90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular [LV] dysfunction), pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock).<sup>316</sup> Rescue thrombolysis or thrombectomy can be considered in patients with hemodynamically stable PE who deteriorate despite anticoagulation.<sup>313,315</sup> For patients with hemodynamic compromise, venoarterial extracorporeal membrane oxygenation (VA-ECMO) can be considered to optimize end-organ function as a bridge to recovery or intervention.<sup>317</sup>

In patients with a contraindication to anticoagulation, an IVC filter, preferably retrievable, should be strongly considered with or without



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embolectomy. The patient should be closely followed for a change in clinical status that would allow anticoagulation to be instituted. Permanent filters should only be considered for rare patients with chronic comorbidities or with permanent contraindication to anticoagulation. Filter placement should be considered if anticoagulation treatment is not possible within 1 month of symptomatic VTE onset.<sup>318</sup>

Embolectomy may be considered in patients with hemodynamic instability who have contraindications to thrombolytic therapy or those who remain unstable following thrombolysis (category 2B).<sup>313,315</sup> Selection of thrombolytic agents and thrombectomy devices should be made based on local expertise and experience.

### *Thrombolytic Therapies/Thrombectomy for PE*

Overall, favorable risk-versus-benefit profiles have not been clearly identified for systemic or CDT/catheter-directed thrombectomy for patients who are hemodynamically stable. In the MAPPET-3 trial, the addition of thrombolysis with alteplase to standard heparin treatment was associated with significantly decreased incidence of in-hospital mortality and clinical deterioration requiring treatment escalation (11% vs. 25%;  $P = .006$ ). However, this difference was due to a higher incidence of clinical instability in the placebo group, as in-hospital mortality rates were similar between treatment groups.<sup>319</sup> The clinical endpoints and other aspects of the design of this trial have also been criticized.<sup>320,321</sup> The PEITHO study, which included patients with cancer, reported significantly less death or hemodynamic decompensation (composite outcome) in patients receiving tenecteplase plus heparin versus placebo plus heparin (2.6% vs. 5.6%; OR, 0.44; 95% CI, 0.23–0.87;  $P = .02$ ). There was no difference in death between the two groups (1.2% vs. 1.8%;  $P = .42$ ), but there was significantly more frequent extracranial bleeding and stroke in the tenecteplase group (6.3% vs. 1.2%;  $P < .001$  and 2.4% vs. 0.2%;  $P = .003$ , respectively).<sup>322</sup> This benefit-to-risk profile is corroborated by results from a

meta-analysis whereby the use of thrombolytic therapy was associated with lower all-cause mortality (OR, 0.53; 95% CI, 0.32–0.88) but higher risk of major bleeding (OR, 2.73; 95% CI, 1.91–3.91).<sup>323</sup> Other meta-analyses reported no significant benefit with thrombolytic therapy compared with heparin alone in terms of recurrent PE or death, particularly for patients with hemodynamically stable PE.<sup>324–328</sup> In the case of CDT, grade II clot lysis was achieved in a similar proportion of patients with cancer and those without cancer with no significant difference in bleeding risk in a retrospective consecutive case series.<sup>329</sup> Reports from several studies evaluating the use of pulmonary embolectomy provide support for the use of this procedure in patients with hemodynamically stable or unstable acute PE characterized by RV dysfunction.<sup>330–332</sup> It must be noted, however, that none of these studies specifically address patients with cancer. In a small, randomized trial, US-assisted CDT was shown to reverse RV dilatation in patients with hemodynamic stability. For PE, however, there was no difference in mortality or recurrent VTE.<sup>333</sup> Larger randomized studies with clinical outcomes are needed to confirm the benefits of this approach.

### *IVC Filters for DVT/PE*

IVC filter usage has increased substantially in the last few decades; however, due to the lack of randomized controlled trials evaluating their safety and efficacy, no particular filter should be considered superior.<sup>334–336</sup> Moreover, IVC filters have been associated with an increased risk for recurrent DVT.<sup>337–339</sup> The pivotal PREPIC trial, which compared permanent IVC filters in conjunction with anticoagulation with anticoagulant therapy alone, did not test the efficacy of IVC filters in the usual clinical scenario in which they are used, which is in patients without concomitant anticoagulation.<sup>337,338</sup> In the PREPIC II study of retrievable IVC filters, there was no difference in recurrent PE between patients treated with anticoagulation and filters compared with anticoagulation alone (3% vs. 1.5%; RR, 2.0; 95% CI, 0.51–7.89).<sup>340</sup> In a multicenter trial of IVC filters in

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patients severely injured following major trauma, filters did not reduce the incidence of symptomatic PE or death compared to no filter (13.9% vs. 14.4%; HR, 0.99; 95% CI, 0.51–1.94;  $P = .98$ ).<sup>341</sup> Until further data are available, IVC filter placement should only be considered for patients with acute proximal lower-extremity DVT or PE who have absolute contraindications to anticoagulation. The benefit of placing an IVC filter in the absence of a lower-extremity IVC or pelvic DVT is unclear. IVC filters should only be used in patients in whom the benefits outweigh the risks, and filters should be retrieved as soon as possible.

### Evaluation and Treatment of Splanchnic Vein Thrombosis

Splanchnic vein thrombosis (SPVT) refers to a relatively rare group of VTE within the splanchnic vasculature comprising the hepatic (characteristic of Budd-Chiari syndrome), portal, mesenteric, and splenic veins. The presence of SPVT has been associated with decreased survival in patients with cancer. In particular, portal vein thrombosis has been reported in about 20% to 30% of patients with hepatocellular carcinoma at the time of diagnosis and is an independent predictor of poor survival.<sup>342-345</sup> Thrombotic events may occur in multiple segments or in isolated segments within the splanchnic vasculature, with isolated portal vein thrombosis being the most common.<sup>346,347</sup> Thrombosis in multiple segments has been associated with significantly decreased 10-year survival rate compared with thrombosis in a single/isolated segment (48% vs. 68%;  $P < .001$ ).<sup>347</sup> In a retrospective study in patients with extrahepatic portal vein thrombosis, a concurrent diagnosis of mesenteric vein thrombosis was significantly predictive of decreased survival, as well as the presence of cancer.<sup>348</sup> Several smaller retrospective studies have also reported adverse outcomes for patients with mesenteric vein thrombosis, with a 30-day mortality rate of 20%.<sup>349,350</sup> Thromboses in the mesenteric vein can lead to intestinal infarction, which is frequently life-threatening.<sup>349,350</sup> Intestinal infarction has been reported in 30% to 45%

of these patients at the time of diagnosis, of which up to 19% were fatal.<sup>346,349</sup>

### Risk Factors

Risk factors for SPVT relevant to patients with cancer include recent abdominal surgery (eg, splenectomy),<sup>351-354</sup> abdominal mass/cancer (hepatobiliary, luminal GI, pancreatic cancers), pancreatitis,<sup>355</sup> cirrhosis,<sup>348</sup> paroxysmal nocturnal hemoglobinuria (PNH),<sup>356</sup> myeloproliferative disorders,<sup>357</sup> and *JAK2V617F* mutation with or without overt myeloproliferative disorders.<sup>358,359</sup> In addition, the use of exogenous estrogen, such as oral contraceptives or hormone replacement therapy, has also been linked to SPVT.<sup>348,360</sup> The presence of cancer itself, especially abdominal malignancies, is both a common risk factor for SPVT and a frequent cause of death in patients with SPVT.<sup>347-350</sup> The *JAK2V617F* mutation is detected in a high proportion of patients with polycythemia vera, essential thrombocythemia, and primary myelofibrosis, and now constitutes a part of both diagnostic and prognostic assessment of these myeloproliferative disorders.<sup>361-364</sup> In the absence of overt myeloproliferative disorders, *JAK2V617F* has been detected in approximately 20% to 40% of patients with SPVT.<sup>365-367</sup> Mutations in exon 12 of *JAK2* may also be associated with SPVT in patients without *JAK2V617F*.<sup>368</sup> PNH is a rare acquired clonal hematopoietic disorder resulting in chronic hemolysis, and has been associated with a high propensity for venous thrombosis, particularly in the splanchnic vasculature.<sup>369,370</sup> In a *post hoc* analysis of patients with Budd-Chiari syndrome, those who had underlying PNH more frequently presented with additional SPVT at baseline compared to patients without PNH (47% vs. 10%;  $P = .002$ ).<sup>371</sup>

### Evaluation

Clinical manifestations of acute SPVT typically include abdominal pain or mid-abdominal colicky pain, abdominal distention, rebound tenderness,



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guarding, fever, anorexia, nausea, vomiting, diarrhea, GI bleeding, hepatomegaly, and ascites.<sup>372-376</sup> SPVT may also be an incidental finding. Rebound tenderness, guarding, and fever may be indicative of progression to bowel infarction.<sup>372</sup> Chronic SPVT may often be asymptomatic due to formation of collateral veins,<sup>372,373,377,378</sup> although abdominal pain, nausea, vomiting, anorexia, lower-extremity edema, and splenomegaly have been reported with chronic presentations.<sup>373,376</sup> Weight loss, abdominal distension, and postprandial abdominal pain may also be associated with chronic mesenteric vein thrombosis.<sup>377</sup> Presence of splenomegaly and/or esophageal varices is a sign of portal hypertension associated with chronic SPVT, and complications may arise due to bleeding from varices.<sup>373,377,379,380</sup> Acute SPVT is associated with presenting signs or symptoms of up to 8-week duration, with no portal cavernoma and no signs of portal hypertension.<sup>374</sup>

The diagnostic evaluation includes medical H&P, based on which further diagnostic testing involving both laboratory testing and imaging can be considered. Additional workup consists of CBC with platelet count and differential, PT, aPTT, basic metabolic profile, hepatic profile, and serum lactate levels. Imaging modalities include abdominal duplex US, CT abdomen/pelvis with contrast, and abdominal MRI with contrast. For suspected cases of SPVT involving the hepatic and/or portal veins, duplex ultrasonography is considered the initial choice of imaging.<sup>366,378-380</sup> CT abdomen/pelvis with contrast is the preferred imaging study for patients with suspected mesenteric vein thrombosis as duplex US can be limited by overlying bowel gas.<sup>372,380</sup> In the case of negative or indeterminate imaging results, other causes should be investigated. If there is continued suspicion of SPVT, repeat imaging is recommended, with consideration of consultation with radiology to optimize imaging techniques/modality.

## Treatment

### Acute Hepatic Vein Thrombosis

Acute hepatic vein thrombosis is defined by the presence of symptoms for ≤8 weeks. Patients with no contraindication to anticoagulation should undergo anticoagulant therapy with hepatology evaluation. Catheter-directed pharmacomechanical thrombectomy with or without transjugular intrahepatic portosystemic shunt (TIPS) should be considered (see *Thrombolytic Agents and Contraindications to Thrombolysis and Indications for Thrombolysis* in the algorithm). TIPS should be considered as one of the treatment options for patients with SPVT and severe symptoms or evidence of portal hypertension. If thrombectomy expertise is not available, consultation with a tertiary medical center is recommended. The decision to offer thrombolysis should be based on local availability/expertise, location of thrombus, and risk of bleeding. The choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. In the presence of contraindications to anticoagulants, patients should undergo hepatology evaluation, be considered for TIPS or surgical shunt, and regularly be reassessed for contraindications to anticoagulation.

### Chronic Hepatic Vein Thrombosis

Chronic hepatic vein thrombosis is defined by the presence of symptoms for >8 weeks. Patients should undergo hepatology evaluation and be considered for TIPS (in the setting of portal hypertension) or surgical shunt and anticoagulation. It must be noted that risks/benefits of anticoagulation must be carefully weighed in patients with chronic thrombosis. The duration of anticoagulation should be at least 6 months for triggered events (eg, postsurgical) and indefinite if active cancer, persistent thrombophilic state, or unprovoked thrombotic event is present.



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### *Acute Portal, Mesenteric, and/or Splenic Vein Thrombosis*

An acute thrombotic event is defined by the presence of symptoms for  $\leq 8$  weeks, with no cavernous transformation/collaterals and no signs of portal hypertension. Anticoagulation and catheter-directed pharmacomechanical thrombectomy with or without TIPS is recommended for patients with no contraindication to anticoagulation with the same considerations as in those with acute hepatic vein thrombosis. Additionally, acute thrombosis involving the mesenteric veins is associated with high risks of intestinal infarction, which is life-threatening and requires immediate surgery to resect necrotic sections of the bowel.<sup>346,349</sup> In the presence of contraindication to anticoagulants, patients should regularly be reassessed for contraindications to anticoagulation, similar to those with hepatic vein thrombosis, as well as GI/surgery evaluation and subsequent surgery if bowel infarction is present.

### *Chronic Portal, Mesenteric, and/or Splenic Vein Thrombosis*

Chronic thrombosis is defined by the presence of symptoms for longer than 8 weeks or cavernous transformation/collaterals or signs of portal hypertension at the time of diagnosis. Patients should be considered for GI evaluation and surgery if bowel infarction is present,  $\beta$  blockers, variceal banding or sclerosis, and TIPS or surgical shunt and anticoagulation with the same considerations as those with chronic hepatic vein thrombosis.

### *Anticoagulation for SPVT*

Anticoagulation as initial and long-term therapy in patients with SPVT has been reported in several studies.<sup>346,357,375,381</sup> In a study of patients with acute SPVT primarily treated with anticoagulation (LMWH for 7–10 days followed by oral anticoagulation for 6 months), 45% of patients experienced complete recanalization. Patients requiring resection for intestinal infarction, experiencing incomplete recanalization of thrombus, or having inherited thrombophilia were given lifelong oral anticoagulation in this study. Recurrent VTE occurred in 18.5% of patients overall, and

only in those who did not receive anticoagulation, and was significantly more frequent among patients with concurrent myeloproliferative disorders at presentation versus those without (70% vs. 13%;  $P < .0001$ ).<sup>346</sup> In a prospective multicenter study in patients with acute portal vein thrombosis treated with anticoagulation (initial therapy with heparin followed by oral anticoagulation for 6 months or long-term in patients with permanent prothrombotic disorders or obstruction of mesenteric vein), the 1-year recanalization rates in the portal vein, mesenteric vein, and splenic vein were 38%, 61%, and 54%, respectively.<sup>375</sup>

Anticoagulation appears to lower the risk for recurrent thrombosis in patients with SPVT without increasing the risk for severe bleeding,<sup>346,357,375,381</sup> including in patients with underlying prothrombotic states.<sup>357</sup> An individual-patient meta-analysis of the effectiveness and safety of anticoagulation for SPVT revealed lower risks of VTE recurrence (HR, 0.42; 95% CI, 0.27–0.64), major bleeding (HR, 0.47; 95% CI, 0.30–0.74), and mortality (HR, 0.23; 95% CI, 0.17–0.31) during anticoagulation therapy compared to off-treatment periods.<sup>382</sup> The study did include patients with cancer (32% of patients had solid cancers, 7.2% had myeloproliferative neoplasms, and 1.2% had leukemia, lymphoma, or multiple myeloma).

In contrast, a large, retrospective cohort study did not find evidence that anticoagulation was beneficial for the prevention of recurrent thrombosis in patients with SPVT. The rate of recurrent VTE was not significantly improved with oral warfarin in terms of 10-year recurrence-free survival rate (89% vs. 77% in the control group;  $P = .38$ ). Hormone therapy was the only independent predictor of recurrence in this study. Moreover, major bleeding events were reported more frequently among patients receiving anticoagulation compared with those who did not (26% vs. 19%;  $P < .05$ ), with gastroesophageal varices and anticoagulation as independent predictors of bleeding.<sup>347</sup> In chronic SPVT, the presence of portal





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hypertension may increase the risk of bleeding from esophageal varices and splenomegaly may lead to decreased platelet counts, which can further increase the risks of bleeding events in patients treated with anticoagulation.<sup>383</sup> Thus, in the absence of randomized controlled trials, the issue of long-term or lifelong anticoagulation remains somewhat controversial in patients with SPVT. An individual's risk factor(s) for SPVT should be taken into consideration when weighing the risks and benefits of long-term anticoagulation.

### *Catheter-Directed Thrombolytic Therapy for SPVT*

Thrombolytic therapy may be most suitable when administered locally for patients with recent thrombosis; however, this approach should be used with caution due to risks for major bleeding complications.<sup>384-387</sup> TIPS may be appropriate for patients with an occluded IVC or a portacaval pressure gradient <10 mmHg, and in those with refractory ascites and progressive hepatic dysfunction.<sup>388,389</sup> This procedure is less invasive than surgical interventions, and has been successful in reducing portal hypertension, resolving ascites, and improving hepatic function in patients with Budd-Chiari syndrome.<sup>388-393</sup> Although shunt dysfunction or stenosis is common during follow-up, TIPS is associated with promising long-term outcomes, with 5-year transplant-free survival rates of 74% to 78%.<sup>388,393</sup> On the other hand, surgical portosystemic shunts may be appropriate in patients without an occluded IVC, with a portacaval pressure gradient >10 mmHg, and with preservation of hepatic function.<sup>394</sup> The impact of surgical shunts versus other interventions on long-term outcomes is unknown<sup>395</sup>; nevertheless, 5-year survival rates range from 75% to 87% in patients with Budd-Chiari syndrome undergoing successful surgical portosystemic shunts.<sup>396-398</sup> This procedure may improve survival outcomes in patients with intermediate-risk prognostic factors as defined by Darwish Murad et al.<sup>399</sup> Of note, surgical shunts appear to have now largely been replaced with TIPS.<sup>389</sup>

### *β-Blockers and Endoscopic Treatments for SPVT*

Gastroesophageal varices may be seen in 35% to 50% of patients with portal vein thrombosis at presentation and remain a significant independent risk factor for major bleeding in patients with SPVT.<sup>347</sup> β-blockers and endoscopic treatments have been evaluated for variceal bleeding in patients at high risk of bleeding events. Even though one study showed visceral banding ligation to be more effective than propranolol in preventing visceral bleeding in patients with cirrhosis with high-risk gastroesophageal varices (7% vs. 30%;  $P = .043$ ),<sup>400</sup> results from several prospective randomized studies found these options to be equally effective (12%–25% vs. 24%–29%), with similar overall mortality rates.<sup>401-403</sup> In one study, ligation was associated with a significantly decreased incidence of esophageal variceal bleeding compared with propranolol (5% vs. 25%;  $P = .027$ ) at the expense of a higher incidence of subcardial variceal bleeding (8% vs. 0%;  $P = .027$ ).<sup>401</sup> Combining the two modalities did not significantly reduce the risks of bleeding (actuarial probability, 7% vs. 11%;  $P = .72$ ) or death (actuarial probability, 8% vs. 15%;  $P = .37$ ).<sup>404</sup> In the context of secondary prophylaxis in patients with noncirrhotic portal hypertension, the incidence of recurrent variceal bleeding was similar between patients receiving ligation versus propranolol (24% vs. 18%;  $P = .625$ ).<sup>405</sup> However, a meta-analysis of randomized studies demonstrated that the combined modality was significantly more effective than endoscopic treatment alone in preventing overall recurrent bleeding (OR, 2.20; 95% CI, 1.69–2.85;  $P < .0001$ ) and in decreasing overall mortality (OR, 1.43; 95% CI, 1.03–1.98;  $P = .03$ ). These data suggest that a combined regimen may be preferred as secondary prophylaxis for esophageal variceal bleeding.<sup>406</sup>

### **Therapeutic Anticoagulation for VTE in Patients with Cancer**

The only placebo-controlled, randomized clinical trial on the use of anticoagulants, in particular heparin followed by warfarin, to treat VTE was performed in 1960.<sup>407</sup> Although most of the subsequent clinical trials

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evaluating the use of anticoagulation therapy in the prevention and treatment of VTE have not been placebo-controlled, the evidence supporting the effectiveness of such therapies is strong.<sup>408-412</sup>

Anticoagulation agents used in the treatment of VTE are listed in *Therapeutic Anticoagulation for VTE* in the algorithm. U.S. Food and Drug Administration (FDA) indications and NCCN recommendations for these therapies are listed in the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Venous Thromboembolic Disease (for the latest version of the NCCN Compendium, please visit [www.NCCN.org](http://www.NCCN.org)). The Panel recommends that agent selection be based on the presence of renal insufficiency, hepatic disease, inpatient/outpatient status, FDA approval, cost, patient preference, ease of administration, need for therapeutic monitoring, bleeding risk assessment, and reversibility. Suggested dosing schedules were established according to Panel consensus and follow, with several exceptions, manufacturer recommendations. To avoid potential conflicts, users can consult dosing schedules listed in specific institutional standard operating procedure (SOP) documents. Recommendations of the American College of Chest Physicians (ACCP) provide another legitimate source for anticoagulant dosing schedules.<sup>152,313,413-415</sup>

### Direct Oral Anticoagulants

Apixaban is an orally administered direct Factor Xa inhibitor approved by the FDA for a variety of indications, including the prevention and initial short- and long-term treatment of VTE.<sup>416-418</sup> Since apixaban is primarily metabolized in the liver and renal elimination accounts for only about 27% of total drug clearance, the drug should be avoided in patients with severe hepatic impairment.<sup>418</sup> Several clinical trials have found apixaban and LMWHs to be equivalent options for the treatment of VTE.<sup>419-422</sup> In fact, apixaban led to lower or similar rates of recurrent VTE compared to dalteparin in the ADAM VTE trial and the Caravaggio study (0.7% vs. 6.3%; HR, 0.099; 95% CI, 0.013–0.780;  $P = .0281$  and 5.6% vs. 7.9%;

HR, 0.63; 95% CI, 0.37–1.07;  $P < .001$  for noninferiority).<sup>420,421</sup> Major bleeding was comparable in both studies and was not higher in the apixaban group.<sup>420-422</sup> The AMPLIFY trial reported a similar rate of recurrent VTE and lower rate of major bleeding in the apixaban group compared to the enoxaparin/warfarin group (3.7% vs. 6.4%; RR, 0.56; 95% CI, 0.13–2.37 and 2.3% vs. 5.0%; RR, 0.45; 95% CI, 0.04–0.78).<sup>419</sup> Moreover, the recent API-CAT trial investigated the extended treatment of patients with active cancer and VTE with reduced-dose apixaban and revealed noninferior outcomes as compared to full-dose apixaban for the prevention of recurrent VTE in this patient population.<sup>423</sup> A lower incidence of clinically relevant bleeding complications was also observed as compared to the full dose.<sup>423</sup> Thus, the Panel recommends consideration of this lower dose after 6 months of therapy and assessments of the patients risk for recurrent VTE and bleeding.

Edoxaban is an orally administered direct Factor Xa inhibitor approved by the FDA for the treatment of DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.<sup>424</sup> Renal clearance accounts for approximately 50% of the total clearance of edoxaban.<sup>425</sup> Clinical trial results indicated edoxaban to be noninferior to dalteparin with respect to the composite outcome of recurrent VTE or major bleeding (12.8% vs. 13.5%; HR, 0.97; 95% CI, 0.70–1.36;  $P = .006$  for noninferiority;  $P = .87$  for superiority).<sup>426</sup> It must be noted that edoxaban therapy is initiated after initial therapy with LMWH or UFH for at least 5 days. Dabigatran, another DOAC, follows a similar treatment regimen.<sup>427</sup> Renal clearance of dabigatran is 80% of total clearance after oral administration.<sup>427</sup> The clinical benefit of dabigatran in the treatment of cancer-associated VTE was found to be equivalent to warfarin in terms of both efficacy (HR, 0.75; 95% CI, 0.20–2.8 at baseline and HR 0.63; 95% CI, 0.20–2.0 for cancer diagnosed during the study) and safety (major bleeding HR, 4.1; 95% CI 2.2–7.5).<sup>428</sup> However, unlike warfarin, concurrent administration with parenteral anticoagulants is not recommended when transitioning to

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edoxaban or dabigatran. Prescribing information must be consulted for transitioning protocols between agents.

Rivaroxaban is an orally administered direct Factor Xa inhibitor approved by the FDA for a variety of indications, including the prevention and treatment of VTE.<sup>429-431</sup> The drug is primarily eliminated via the kidneys; thus, rivaroxaban should be avoided in patients with severe renal impairment and used with caution in those with moderate impairment.<sup>431</sup> Subgroup analysis of the EINSTEIN-DVT and EINSTEIN-PE trials in patients with active cancer concluded that rivaroxaban had similar efficacy to prevent VTE recurrence (5% vs. 7%; HR, 0.67; 95% CI, 0.35–1.30) and reduce major bleeding events (2% vs. 5%; HR, 0.42; 95% CI, 0.18–0.99) compared with enoxaparin and vitamin K antagonist.<sup>432</sup> A prospective cohort study reported the 6-month cumulative incidence of new or recurrent VTE to be 4.4% and major bleeding to be 2.2% in patients on rivaroxaban, which were comparable to the EINSTEIN subgroup analysis.<sup>433</sup> Another clinical trial comparing rivaroxaban and dalteparin had similar outcomes, with 6-month cumulative VTE recurrence rates of 4% and 11% (HR, 0.43; 95% CI, 0.19–0.99), as well as major bleeding rates of 6% and 4% (HR, 1.83; 95% CI, 0.68–4.96) in each respective group.<sup>434</sup>

Based on the quality of evidence presented on apixaban and edoxaban, which include data from large (N > 1000) prospective randomized controlled clinical trials,<sup>419,426</sup> the NCCN Panel assigns category 1 recommendations to these agents in the DVT/PE setting. Although stage IV chronic kidney disease is not listed as a contraindication in the FDA-approved label for apixaban, the NCCN Panel acknowledges that there are observational data to support safe apixaban dosing in this setting, especially in the setting of hemodialysis. Apixaban, edoxaban, and rivaroxaban are preferred options for patients without gastric or gastroesophageal lesions as patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with DOACs and thus,

LMWHs are preferred in this setting. In the Hokusai VTE Cancer Study, the absolute rate of recurrent VTE was found to be 3.4% lower with edoxaban compared to dalteparin, whereas the absolute rate of major bleeding was 2.9% higher. In particular, the excess of major bleeding with edoxaban was confined to patients with GI cancer.<sup>435</sup> On the other hand, results from the Caravaggio study demonstrated that major bleeding occurred in comparable proportions of patients treated with apixaban or dalteparin (3.8% vs. 4.0%). Of note, major bleeding occurred in nine patients with GI cancer in each treatment group.<sup>436</sup> Thus, the NCCN Panel postulates that apixaban may be safer than edoxaban or rivaroxaban for patients with gastric or gastroesophageal lesions (category 2B recommendation).

A recent retrospective study compared the safety and efficacy of DOACs versus LMWH for treatment of VTE in patients with primary brain tumors or secondary metastases to the brain.<sup>437</sup> There was no significant difference in 6-month cumulative bleeding events, including intracranial hemorrhage, in the DOAC arm compared to the LMWH arm (14.3% vs. 27.8%;  $P = .10$ ). Similarly, rates of recurrent VTE events were similar between the DOAC and LMWH arms, at 5.6% and 6.6%, respectively ( $P = .96$ ). These data suggest that DOACs may be a safe and effective treatment option for VTE in this patient population.

### Low-Molecular-Weight Heparins

Dalteparin<sup>144</sup> is approved for prevention and treatment of VTE and extended treatment of symptomatic VTE in patients with cancer and enoxaparin<sup>147</sup> is approved by the FDA for the immediate treatment of VTE. A Cochrane review found no significant differences in bleeding, thrombocytopenia, or survival outcomes with LMWH compared with oral vitamin K antagonists for the chronic treatment of VTE in patients with cancer. However, the incidence of VTE was significantly lower for patients receiving LMWH (RR, 0.58; 95% CI, 0.43–0.77).<sup>438</sup> Although each of the



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two LMWHs has been studied in randomized controlled trials in patients with cancer, the efficacy of dalteparin in this population is supported by the highest quality evidence<sup>409,439</sup> and is the only LMWH approved by the FDA for this indication. NCCN-recommended dosing regimens for dalteparin<sup>409,439,440</sup> and enoxaparin<sup>147,408,441,442</sup> in VTE treatment are based on the results of clinical studies and Panel consensus. Dalteparin has been found to be more effective than a coumarin derivative regarding recurrent VTE (8.0% vs. 15.8%; HR, 0.48;  $P = .002$ ) without increasing the risk of bleeding in a large prospective randomized study.<sup>409</sup> Its safety for cancer-associated VTE has also been monitored for a prolonged period (12 months).<sup>439</sup> On the other hand, the efficacy of enoxaparin for patients with cancer has been confirmed in a small study in comparison with warfarin (combined outcome including major bleeding or recurrent VTE: 10.5% vs. 21.1%; 95% CI, 4.3%–20.3%;  $P = .09$ ).<sup>408</sup> In another study, enoxaparin was found to be a safe and effective option either by itself or in combination with warfarin.<sup>441</sup> Additionally, enoxaparin at fixed dosages of 1.0 mg/kg twice daily or 1.5 mg/kg once daily was reported to be equivalent to dose-adjusted UFH in terms of both symptomatic VTE (2.9% and 4.4% vs. 4.1%) and major hemorrhage (1.3% and 1.7% vs. 2.1%) in a large, prospective, randomized trial. However, this study did not specifically enroll patients with cancer<sup>442</sup> and long-term treatment with enoxaparin dosing of 1.0 mg/kg SC every 12 hours has not yet been tested in patients with cancer. Thus, the NCCN Panel assigns a category 1 recommendation to dalteparin for DVT/PE.

Extended anticoagulation therapy with LMWHs may require dosage reduction after an initial period. In the CLOT study, the dalteparin dosing was lowered from 200 units/kg daily to 150 units/kg daily after 1 month.<sup>409</sup> In addition, the European Society for Medical Oncology (ESMO) clinical recommendations for management of VTE in patients with cancer specifies using 75% to 80% of the initial dose of LMWH for extended anticoagulation therapy.<sup>443</sup> Limited evidence exists concerning the safety

and efficacy of LMWHs in special populations, such as patients with renal insufficiency, patients with BMI  $>30$  kg/m<sup>2</sup>, patients weighing  $<50$  kg, patients  $\geq 70$  years of age, and patients with cancer.<sup>444</sup> The NCCN Panel suggests that each institution prepare a LMWH dosing algorithm tailored for these subsets of patients. Of the two LMWHs, specific dosing recommendations for patients with severe renal insufficiency (CrCl  $<30$  mL/min) are available only for enoxaparin.<sup>147,445</sup> These recommendations are supported by results from multiple studies showing reduced renal clearance of enoxaparin and its association with a 2- to 3-fold increase in risk of bleeding when administered in standard, unadjusted therapeutic doses to patients with severe renal insufficiency.<sup>178,446,447</sup> On the other hand, available data suggest dalteparin might be sufficiently cleared in patients with renal impairment<sup>176,448</sup>; however, monitoring of peak anti-Xa levels is still recommended in patients with CrCl  $<30$  mL/min.<sup>144</sup> Of the two LMWHs, a specific dosing recommendation for patients with BMI  $\geq 40$  kg/m<sup>2</sup> is available only for enoxaparin.<sup>449</sup> This recommendation is supported by a randomized controlled trial of enoxaparin 1 mg/kg versus reduced dose of 0.8 mg/kg every 12 hours in patients with BMI  $\geq 40$  kg/m<sup>2</sup>. A similar number of patients in both the reduced-dose arm and standard-dose arm reached goal anti-Xa levels, at 89.3% versus 76.9%, respectively ( $P = .29$ ).<sup>449</sup>

Increased survival rates have been reported for subgroups of patients receiving chronic treatment with LMWH versus other VTE therapies or placebo.<sup>450,451</sup> In the FAMOUS study of patients with advanced cancer without VTE, subgroup analysis of patients with better prognoses suggested that 2- and 3-year survival rates were higher for patients receiving dalteparin compared to those receiving placebo.<sup>450</sup> A post hoc analysis of patients from the CLOT study also indicated that among patients without metastases, 1-year survival rates were higher for those receiving dalteparin versus an oral vitamin K antagonist.<sup>451</sup> Other randomized studies and systematic reviews have provided evidence both





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for and against the purported survival benefits of LMWHs in patient with cancer.<sup>452-457</sup> Of note, two large randomized prospective trials, as well as a systematic review, reported no overall survival advantage in patients with lung cancer receiving LMWH.<sup>455,457,458</sup>

### Fondaparinux

Fondaparinux is a specific indirect Factor Xa inhibitor for the treatment of VTE whose advantages include specific neutralization of factor Xa, elimination of the need to monitor anticoagulant response in most cases, and the lack of cross reactivity with the antibody associated with HIT.<sup>151,415,459</sup> Subgroup analysis of data from the Matisse clinical trials supports the use of fondaparinux in patients with cancer. In these studies, fondaparinux led to a higher 3-month DVT recurrence rate (12.7% vs. 5.4%; absolute difference 7.3%; 95% CI, 0.1–14.5) but a lower PE recurrence rate (8.9% vs. 17.2%; absolute difference, -8.3; 95% CI, -16.7, 0.1) than enoxaparin, with no difference in bleeding or overall survival.<sup>460</sup> The use of fondaparinux in patient populations with renal insufficiency or obesity has not been well-defined, although there is some evidence to support its safe and effective use in patients ≥60 years of age with a broad range of body weights.<sup>153</sup> The NCCN Panel recommends against the use of fondaparinux in patients with severe renal insufficiency and advises caution for use in patients with renal dysfunction (CrCl 30–50 mL/min) and patients >75 years of age. The Panel also recommends a reduced dose in patients weighing <50 kg and an increased dose in those weighing >100 kg.<sup>151,153</sup>

### Unfractionated Heparin

UFH is approved by the FDA for a variety of indications including the treatment of VTE.<sup>461</sup> The initial dosing of UFH in the treatment of VTE is weight-based, with a recommended regimen of 80 units/kg bolus followed by 18 units/kg per hour infusion adjusted to target aPTT or per hospital SOPs.<sup>462</sup> Alternatively, fixed-dose, unmonitored, SC UFH (333 units/kg

load, followed by 250 units/kg every 12 hours) has been reported to be comparable to LMWH in the treatment of patients with acute VTE (recurrent VTE 3.8% vs. 3.4%; absolute difference, 0.4%; 95% CI, -2.6% to 3.3%).<sup>463</sup> Patients receiving IV UFH must be hospitalized and monitored for anticoagulant response. The Panel recommends UFH as the agent of choice in patients with CrCl <30 mL/min, because the liver is a main site of heparin biotransformation.<sup>461</sup> Some exceptions include patients with severe renal dysfunction but without IV access, and those with a new diagnosis of VTE despite therapeutic doses of UFH. In a meta-analysis of trials comparing outcomes with anticoagulants (UFH, LMWH, and fondaparinux) as initial treatment of VTE in patients with cancer, LMWH was associated with a significant reduction in mortality rate at 3-month follow-up compared with UFH (RR, 0.66; 95% CI, 0.40–1.10).<sup>464</sup> However, no significant difference was found in VTE recurrence between LMWH and UFH. Furthermore, no statistically significant differences were found between UFH and fondaparinux in terms of mortality, VTE recurrence, or bleeding events.<sup>465</sup>

### Warfarin

Warfarin is an option for long-term treatment of VTE in patients with cancer following initial treatment/bridging with UFH,<sup>461</sup> LMWH,<sup>144,147</sup> or fondaparinux.<sup>151</sup> Warfarin can be safely administered to patients with renal insufficiency, although the response to warfarin is accentuated in patients with hepatic insufficiency.<sup>466</sup> Warfarin is also the preferred anticoagulant for most patients with APS, especially for those patients with triple-positive APS or lupus inhibitors/anticoagulants. If warfarin is selected for chronic anticoagulation, the NCCN Panel recommends initiating warfarin concurrently with the parenteral agent used for acute therapy (at previously recommended doses) and continuing both therapies for at least 5 days and until the International Normalized Ratio (INR) is ≥2. 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



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measured initially at least once weekly. Once the patient is on a stable dose of warfarin with an INR of 2–3, INR testing can be gradually decreased to a frequency of no less than once monthly. Additionally, it should be noted that the PT/INR can be prolonged by lupus inhibitors/anticoagulants, particularly point-of-care PT/INR. Results across multiple studies suggest that lupus inhibitor/anticoagulant interference is generally not a cause for a concern for most patients treated with common thromboplastins; however, some patients may be affected.<sup>467</sup> New patients should thus be checked for their sensitivity to lupus inhibitors/anticoagulants before they are used to monitor treatment in patients positive for lupus inhibitors/anticoagulants. The PT/INR in patients with a PT that exceeds the upper limit of the reference range will likely have a PT/INR affected by lupus inhibitors/anticoagulants and alternatives should be used.<sup>467</sup> If INR is being monitored by point-of-care devices, the INR results should be used with caution,<sup>467</sup> and most manufacturers of these devices list the presence of lupus inhibitors/anticoagulants as a contraindication to their use. Results of the effects of point-of-care devices on INR remain an area that requires more data and evaluation.

### Contraindications and Risks to Therapeutic Anticoagulation

Contraindications to anticoagulation can be relative or absolute, and temporary or permanent. Consideration of the degree of contraindication to anticoagulation and its duration are essential when evaluating the risks and benefits of anticoagulation (see *Contraindications to Therapeutic Anticoagulation* in the algorithm as well as the table of Contraindications and Warnings under *Therapeutic Anticoagulation for VTE* in the algorithm for contraindications of specific agents). The risks and benefits of anticoagulation and the presence of contraindications must be considered on an individual basis. The Panel recommends frequent re-evaluation of these contraindications and of the risks and benefits of anticoagulation therapy for all patients with cancer.

The use of anticoagulants is complicated by the fact that patients with cancer with VTE have a higher likelihood of developing recurrent VTE and major bleeding than those without malignancy.<sup>60,468</sup> In patients with cancer, bleeding rates were independent of INR values and were high across different INR categories, whereas recurrence rate was lower when the INR was >2.<sup>468,469</sup> In one prospective follow-up study, the 12-month cumulative incidence of major bleeding was 12.4% and 4.9% in patients with and without cancer, respectively (HR, 2.2; 95% CI, 1.2–4.1). In this study, one-third of all cases of major bleeding occurred during the initial 5 to 10 days of heparin, and the risk of bleeding increased with the extent of cancer.<sup>60</sup> Subsequent randomized controlled studies for the chronic treatment of VTE in patients with cancer demonstrated that LMWHs and vitamin K antagonists are associated with a similar incidence of bleeding events, including major bleeding<sup>408–410</sup>; however, in one study, fatal bleeding was reported in 8% of patients receiving vitamin K antagonists compared with none receiving LMWH.<sup>408</sup> Other risks include osteoporosis and HIT for patients receiving heparins, and drug and food interactions for patients receiving vitamin K antagonists. For example, in patients receiving either a vitamin K antagonist or enoxaparin, decreases in bone mineral density of 1.8% and 3.1% at 1-year follow-up, and 2.6% and 4.8% at 2-year follow-up, respectively, were seen.<sup>470</sup>

Warfarin has a very narrow therapeutic window, and its activity is known to be affected by the administration of many other drugs. For example, a number of antibiotics and antifungal therapies, including trimethoprim-sulfamethoxazole, ciprofloxacin, metronidazole, and fluconazole, potentiate the effect of warfarin, whereas other antibiotics such as rifampin and dicloxacillin antagonize the effect of warfarin.<sup>471,472</sup> Furthermore, certain chemotherapeutic agents, such as 5-fluorouracil and capecitabine, are known to increase the INR in patients undergoing warfarin anticoagulation,<sup>473,474</sup> and drug interactions between warfarin and certain selective estrogen receptor modulators (tamoxifen and raloxifene)



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have also been reported.<sup>475</sup> Dietary intake of vitamin K and certain dietary supplements can also influence the effects of warfarin.<sup>476,477</sup> Finally, acetaminophen, found in many medications, can increase the therapeutic effects of warfarin when taken in daily doses exceeding 2 g.<sup>478</sup>

DOACs are absorbed primarily in the stomach and proximal small bowel (with the exception of apixaban, which is also absorbed in the distal small bowel and the proximal colon), so these agents may not be appropriate for patients who have had significant resections of these portions of the intestinal tract. Retrospective cohort studies of patients who had bariatric and cancer GI surgery support that apixaban levels are more likely to remain in the expected peak on treatment range than rivaroxaban after gastric or proximal small bowel resections. Dabigatran levels were below the peak, and limited information exists for edoxaban but in the few patients that have been studied levels were in the expected peak on treatment range.<sup>479-482</sup> For additional information on absorption guidance following GI surgical interventions and enteral feeding tube administration, see *Therapeutic Anticoagulation for VTE: DOACs: GI Considerations and Alternative Routes of Administration* in the algorithm.

### Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia

Thrombocytopenia is a common consequence of cancer treatment; however, little guidance exists regarding anticoagulation usage in this setting in those with a concurrent or recent VTE diagnosis.<sup>483-485</sup> In a small retrospective cohort study evaluating patients with hematologic malignancy and VTE before or during platelet counts dropping below 50,000/ $\mu$ L, withholding anticoagulation resulted in significantly reduced bleeding (3% vs. 27% in those receiving anticoagulation; incidence rate ratio [IRR], 10.1; 95% CI, 1.5–432.6) but significantly increased recurrent VTE (15% vs. 2%; IRR, 0.17; 95% CI, 0.0–1.51).<sup>229</sup> The NCCN Panel considers anticoagulation to be safe with platelet counts  $\geq$ 50,000/ $\mu$ L and

recommends careful weighing of the risks for recurrent thromboembolism and bleeding. Based on this evaluation, patients at high risk can either continue to receive therapeutic dose anticoagulation with platelet transfusions or undergo placement of a retrievable IVC filter and discontinue anticoagulation. It was demonstrated in a small single-institution observational cohort study that 31 of 59 patients receiving anticoagulation and transfusion support for a platelet goal of 50,000/ $\mu$ L experienced bleeding events. Eleven patients experienced transfusion reactions.<sup>486</sup> Therefore, prospective data are needed to identify an optimal transfusion strategy in this setting.

Patients considered at low risk for VTE recurrence can receive a lower dose of anticoagulation, have their CVAD removed in the case of CVAD-associated DVT, or be monitored for distal DVT with serial US surveillance while being off anticoagulation (see *Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia* in the algorithm). In a prospective cohort study, it was demonstrated that a fixed subtherapeutic dose of LMWH was efficient and safe in patients with cancer requiring interruption of long-term vitamin K antagonist therapy due to treatment-induced thrombocytopenia.<sup>487</sup> In a small, single-institution, retrospective review, enoxaparin at the therapeutic dose was found to be safe to continue, especially if the anticipated duration of platelet count  $<$ 50,000/ $\mu$ L was  $<$ 7 days.<sup>488</sup> The NCCN Panel outlines enoxaparin dose modification in the setting of thrombocytopenia and does not recommend use of DOACs for platelet counts  $<$ 50,000/ $\mu$ L due to limited published data.

### Progression or New Thrombosis on Therapeutic Anticoagulation

Progression or new thrombosis on therapeutic anticoagulation is defined as extension of DVT or PE, or new DVT or PE, while on recommended anticoagulation therapy (see *Progression or New Thrombosis on*



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*Therapeutic Anticoagulation* in the algorithm). An early embolism event might not indicate progression or new thrombosis on therapeutic anticoagulation. An initial determination of whether the INR, aPTT, or LMWH anti-Xa value is within the therapeutic range is important for patients with recurrent VTE who are receiving anticoagulation (see Table 1: Therapeutic Range of Anticoagulants in *Progression or New Thrombosis on Therapeutic Anticoagulation* in the algorithm), as well as assurance of adherence to therapy. Testing for HIT and APS should also be considered in these patients. When INR, aPTT, or anti-Xa values are subtherapeutic, the solution is to increase the anticoagulant dose to a therapeutic level. INR or aPTT values may also be subtherapeutic due to reasons other than inadequate anticoagulant dosing. For example, warfarin resistance can be due to genetic variability associated with the enzymatic metabolism of warfarin, concomitant administration of medications that interact with warfarin, or pharmacokinetic and biophysical/physiologic limitations of warfarin therapy.<sup>489,490</sup> In this case, an alternative agent should be considered. Drug-drug interactions should also be considered, especially for DOACs, as polypharmacy can influence drug-metabolizing enzymes or drug transporters and all DOACs are P-glycoprotein substrates.<sup>491</sup>

Progression or new thrombosis on therapeutic anticoagulation can also occur in the setting of therapeutic INR or aPTT values or, in the case of a DOAC, at therapeutic doses. Causes include cancer-related hypercoagulability, such as Trousseau syndrome; HIT; conditions associated with venous stasis, such as vascular compression by tumors or lymphatic masses or stasis associated with IVC filters; and APS.<sup>492,493</sup> Uncontrolled myeloproliferative neoplasms or PNH may also be responsible for this phenomenon with relief of vascular stasis or treatment of MPN/PHN potentially reducing the risk of recurrence. Diagnostic testing to identify the syndromes identified above, when present, is critical to the management of VTE in these settings.<sup>493</sup> In patients with anatomic

compression due to congenital or acquired causes, relief of anatomic compression is essential to aid in preventing recurrent thrombosis, after which time increasing of anticoagulant dose or switching to an alternative agent can be considered, as renal function allows. For example, a switch to LMWH in the setting of progression or new thrombosis on a DOAC or subtherapeutic INR with warfarin therapy is supported by the results of one study in which a low VTE recurrence rate was reported for patients treated with LMWH following the development of recurrent thromboembolism on warfarin therapy<sup>494</sup> (see Table 2: Alternative Anticoagulant Options in Case of Progression or New Thrombosis on Therapeutic Anticoagulation in *Progression or New Thrombosis on Therapeutic Anticoagulation* in the algorithm).

Although progression or new thrombosis on therapeutic anticoagulation can result if the prescribed anticoagulant dose is inadequate, other factors to consider include adherence to self-administered medications and dosing frequency in patients receiving LMWH.<sup>493</sup> For example, a trend toward an increased risk for VTE recurrence was reported in one study of patients with cancer receiving once-daily enoxaparin in the acute therapy setting.<sup>442</sup> Thus, a twice-daily dosing schedule might be a better option in this setting. A dose increase can also be considered for patients experiencing recurrent VTE while receiving anticoagulant therapies whose effects are not typically monitored in the laboratory (eg, LMWH and fondaparinux).<sup>495,496</sup>

### Thrombolytic Agents

Alteplase and reteplase administered via a catheter or in conjunction with a mechanical thrombectomy device are sometimes used to treat large and/or proximal upper-extremity/intrathoracic or lower-extremity DVT. Thrombolysis with catheter-directed therapies for SPVT is limited to case reports and small studies; the NCCN Panel recommends following local institutional protocols in this setting. The thrombolytic options for PE

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include systemic thrombolysis using alteplase, reteplase, or tenecteplase (category 2B) or US-assisted CDT using alteplase.

Catheter-directed delivery of thrombolytic agents directly into the clot has allowed more localized targeting of thrombolytic agents and the use of catheter-based thrombectomy devices to accelerate clot removal. CDT with or without mechanical thrombectomy is associated with significantly higher rates of complete clot lysis than conventional anticoagulation.<sup>497</sup> Different FDA-approved catheters and devices exist; however, no single catheter or device has been proven to be superior to another.<sup>498</sup> The extent of thrombus may be an important factor in device and agent selection as well as the likelihood of success.

Effective clot lysis in patients with DVT has been reported with CDT using urokinase, alteplase, reteplase, and tenecteplase.<sup>499-507</sup> It must be noted that for DVT, a post-procedural imaging study is recommended to confirm the results of thrombolysis. A retrospective patient series has demonstrated that patients with cancer can benefit from catheter-directed pharmacomechanical thrombolysis.<sup>329</sup> Other studies also postulated that thrombolysis led to fewer post-thrombotic complications compared with anticoagulation alone (mostly heparin) for patients with DVT.<sup>508-511</sup> However, later data are contradictory regarding this matter. In the CaVenT study, PTS was reported in significantly fewer patients in the CDT arm versus the control arm at 24-month follow-up (41% vs. 56%;  $P = .047$ ).<sup>502,503</sup> However, the ATTRACT trial, a multicenter randomized study, reported no significant difference in PTS between patients receiving pharmacomechanical CDT and anticoagulation versus those receiving anticoagulation alone.<sup>512</sup> The NCCN Guidelines do not recommend routine use of CDT over anticoagulation alone but suggest that patients with the following factors are most likely to benefit from CDT: iliofemoral DVT; symptom duration <14 days; good functional status; life expectancy of ≥1 year; and low risk of bleeding.<sup>313,513</sup> The NCCN Panel believes that CDT

and thrombectomy can be considered as a therapeutic option for select patients with limb-threatening/life-threatening acute proximal DVT, particularly when there has been no response to conventional anticoagulation.<sup>315</sup>

In the setting of acute intermediate-risk (submassive) PE, two randomized controlled trials comparing alteplase and tenecteplase to anticoagulation have shown that systemic thrombolysis does not reduce mortality but is associated with an increased risk of bleeding complications.<sup>322,514</sup> In the MOPPET trial, alteplase in conjunction with anticoagulation was shown to be more efficacious in reducing pulmonary hypertension and recurrent PE at 28 months compared to anticoagulation alone (16% vs. 63%;  $P < .001$ ).<sup>514</sup> In the PEITHO study, patients with intermediate-risk PE were randomized to tenecteplase plus anticoagulation or placebo plus anticoagulation. Death or hemodynamic decompensation occurred in 13 of 506 patients (2.6%) in the tenecteplase group compared to 28 of 499 (5.6%) in the placebo group (OR, 0.44; 95% CI, 0.23–0.87;  $P = .02$ ). However, the difference between groups was due to a reduced rate of hemodynamic decompensation in the tenecteplase group. Mortality was similar between groups at day 7 and day 30. Extracranial bleeding (32 patients, 6.3% vs. 6 patients, 1.2%;  $P < .001$ ) and stroke (12 patients, 2.4% vs. 1 patient, 0.2%;  $P = .003$ ) were more common with tenecteplase.<sup>322</sup> Therefore, systemic thrombolytic therapy is reserved for patients with high-risk massive PE.

US-assisted CDT using alteplase has been used for patients with PE<sup>515,516</sup> with ≥50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressure (mean pulmonary artery pressure ≥25 mmHg) or echocardiographic evaluation. Alteplase is administered at a rate of 1 mg/h per drug delivery catheter (2 mg/h for bilateral PE) and infused for 24 hours with one catheter and 12 hours for two catheters.<sup>517</sup> Other

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US-assisted CDT regimens have been tested, supporting this method's utility in the treatment of acute massive and submassive PE.<sup>333,518</sup>

Similar to anticoagulation, contraindications to thrombolysis include absolute and relative contraindications (see *Contraindications to Thrombolysis and Indications for Thrombolysis* in the algorithm).<sup>313</sup> The risks and benefits of thrombolysis should be assessed on a case-by-case basis by the clinician. The use of a thrombolytic agent may be considered in patients who are pregnant and lactating and with life-threatening thrombosis. Studies examining the safety of thrombolytic therapy during pregnancy or lactation are not available, but thrombolytic agents are unlikely to cross the placenta or transfer to breast milk due to their large molecular weight. Besides the indications mentioned above (limb-threatening/life-threatening acute proximal DVT, symptomatic iliofemoral thrombosis, and massive/life-threatening PE), thrombolysis is also indicated for intestinal SPVT with high risk of ischemia.<sup>519</sup>

### Elements to Consider in Decision Not to Treat

The feasibility of invasive or aggressive intervention is not the only consideration for VTE prophylaxis and treatment in patients with cancer.<sup>520</sup> The risks and probability of success of the interventions should be considered as well. Factors to consider before implementing anticoagulation therapy include patient non-acceptance, lack of therapeutic advantage or palliative benefits, whether anticoagulation is associated with an unreasonable burden, and end-of-life/comfort care. Likewise, careful consideration of these issues is also very important in deciding to withhold or withdraw VTE therapy (see *Elements for Consideration in Decision Not to Treat* in the algorithm).

### Reversal of Anticoagulation

In the event of life-threatening bleeding, or the need for urgent/emergent invasive procedures, anticoagulant effects must be promptly reversed. It

should be noted that all anticoagulation reversal products are associated with a risk of thromboembolism. It is recommended that institutions have treatment pathways or guidelines for the reversal of anticoagulation.

The anticoagulant effects of UFH are fully reversible with protamine sulfate, and the anti-Xa activity of LMWHs are partially reversed by protamine sulfate (up to 60%–75% depending on the LMWH). This agent must be used with caution because it can cause anaphylactic reactions, particularly if administered too rapidly, as well as significant hypotension, bradycardia, and pulmonary hypertension. Thus, close monitoring of blood pressure, heart rate, and oxygenation is recommended during administration. Patients with fish allergies and previous exposure to protamine (eg, neutral protamine Hagedorn [NPH] insulin) are at increased risk for allergic reactions as well as those who had a vasectomy or individuals assigned male at birth who are infertile.

IV recombinant human coagulation Factor VIIa (rhFVIIa), which rapidly induces thrombin generation, has been shown to reduce the anticoagulant effects of direct thrombin inhibitors (DTIs) and fondaparinux in laboratory tests.<sup>413,521-528</sup> Although evidence from published studies is limited, available data from *in vitro* models and healthy volunteers support the use of rhFVIIa for management of severe bleeding events with fondaparinux.<sup>413,521-523</sup> Activated prothrombin complex concentrate (aPCC) has also been evaluated as a potential option for reversing the effects of DTIs by improving hemostatic capacity.<sup>527,529-532</sup> The DTIs bivalirudin and dabigatran can be removed with hemofiltration and hemodialysis, although clinical data supporting this approach are limited.<sup>526,533,534</sup> Activated charcoal may also be considered for reversal of dabigatran, especially within a few hours of overdose.<sup>535</sup> Idarucizumab was tested and shown in a large, prospective clinical trial to reverse the anticoagulant effects of dabigatran within minutes in both patients who had uncontrolled bleeding and those who were about to undergo an urgent procedure (median



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maximum percentage reversal 100%; 95% CI, 100–100). Thromboembolic events occurred in 6.3% to 7.4% of patients by day 90.<sup>536,537</sup> Reversal should be monitored by aPTT for DTIs, but dabigatran can also be monitored with diluted thrombin time or Hemoclot thrombin inhibitor test. Overall, limited information is available on the clinical efficacy of all of these proposed reversal strategies. For life-threatening bleeding, the NCCN Panel currently favors the use of rhFVIIa for bivalirudin reversal and aPCC or rhFVIIa for argatroban reversal and dabigatran reversal as first-line agents.

As for the oral direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, the prescribing information indicates that activated charcoal may be considered for reduction of drug absorption, if within 2 hours of ingestion.<sup>418,424,431</sup> Due to the high plasma protein binding, these agents are not expected to be dialyzable. However, andexanet alfa and prothrombin complex concentrate (PCC), specifically 4-factor PCC, are widely used options for reversal of anticoagulation for DOACs. Andexanet alfa was shown in prospective, randomized trials to be a safe and effective option for the reversal of rivaroxaban and apixaban.<sup>538-540</sup> In the small ANNEX-A and the ANNEXA-R clinical trials, apixaban activity was reduced by 94% among those who received andexanet bolus, compared with 21% among those who received placebo ( $P < .001$ ). Rivaroxaban activity was reduced by 92% among those who receive andexanet bolus, versus 18% among those who received placebo ( $P < .001$ ).<sup>539</sup> In the larger ANNEXA-4 trial, among patients who had acute major bleeding, predominantly intracranial or GI, apixaban and rivaroxaban activity both decreased by 92% after andexanet bolus.<sup>540</sup> Andexanet alfa for edoxaban reversal has been examined in healthy volunteers<sup>541,542</sup> and more recently, in patients with acute major bleeding, primarily intracranial.<sup>543</sup> Initial data from this study indicated a median decrease of 69.2% (95% CI, 25.5%–80.2%) in anti-factor Xa activity and 75% excellent or good hemostasis at 12 hours in all patients, and 81.3% in those with intracranial hemorrhage.<sup>543</sup> The

recent ANNEXA-I trial sought to assess andexanet safety and efficacy in patients with acute cerebral hemorrhage with a total of 263 patients receiving andexanet and 267 patients receiving usual care.<sup>544</sup> Of the patients receiving usual care, a majority (85.5%) received PCC. The primary endpoint, hemostatic efficacy, was assessed in an interim analysis of 452 patients and showed that 150 of the 224 patients (67%) receiving andexanet achieved hemostatic efficacy while 121 of the 228 patients (53.1%) receiving usual care achieved hemostatic efficacy, suggesting better control over hematoma expansion with andexanet as compared to usual care.<sup>544</sup> However, andexanet treatment was associated with thrombotic events which occurred in 27 of 263 patients (10.3%) as opposed to 15 of 267 patients (5.6%) that received usual care.<sup>544</sup> Four-factor PCC has been approved for bleeding management in patients receiving warfarin, and despite the development of a recombinant factor Xa, 4-factor PCC continues to be a cost-effective, off-label, non-specific option for reversal of DOACs. Data from *in vivo* models and healthy volunteers suggest that PCC may at least partially reverse the anticoagulation effects of DOACs.<sup>545-547</sup> Additionally, a small, single-center, retrospective study indicated that use of 4-factor PCC emergently reverses rivaroxaban and apixaban effects.<sup>548</sup> In light of these data, both PCC and andexanet alfa can be considered as first-line agents for reversal of DOACs in the setting of life-threatening bleeding. Agent selection should be determined on a case-by-case basis after considering the location of the bleed, the patient's clinical condition, and the risk of thrombotic complications associated with the reversal agent. For andexanet alfa dosing and administration, see *Andexanet Alfa Dosing and Administration* in the *Reversal of Anticoagulation* section of the algorithm. Drug-specific anti-Xa assays should not be used to assess reversal of direct factor Xa inhibitors after administration of andexanet alfa, as they are not interpretable.



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The management of a supratherapeutic INR during treatment with warfarin is a common clinical challenge. In many cases, the effects of warfarin therapy in the patient with an elevated INR who is not bleeding can be reversed by withholding or reducing the warfarin dose, and, depending on the INR, the addition of small doses of oral vitamin K<sub>1</sub> for patients who are thought to be at higher risk of bleeding.<sup>466,549-551</sup> It should be noted that a randomized placebo-controlled trial that included 8% of participants with active cancer did not demonstrate any reduction in bleeding or thromboembolic complication with 1.25 mg oral vitamin K for INR reversal in patients without symptoms (with an INR of 4.5–10).<sup>552</sup> Therefore, use of oral vitamin K should be considered on a case-by-case basis. Consistent with the 2012 ACCP Guidelines, the NCCN Panel recommends the use of oral vitamin K (1–2.5 mg) for patients with an INR >10 on warfarin, and who have no evidence of bleeding<sup>551</sup> (see *Reversal of Anticoagulation* in the algorithm).

For patients requiring rapid warfarin reversal for urgent or emergent surgical procedures, IV administration of vitamin K<sub>1</sub> is preferred over oral vitamin K<sub>1</sub>. In a prospective randomized study that compared INR outcomes with IV (0.5 mg) or oral (2.5 mg) vitamin K<sub>1</sub> in patients with baseline INR 6–10 on warfarin, a greater proportion of patients in the IV therapy arm achieved rapid therapeutic INR (2–4) at 6 hours (46% vs. 0%) and at 12 hours (67% vs. 35%) compared with oral therapy.<sup>553</sup> In a prospective study that evaluated vitamin K<sub>1</sub> in patients requiring rapid warfarin reversal for elective surgery, IV vitamin K<sub>1</sub> resulted in an INR ≤1.5 on the day of surgery in nearly all patients (94%).<sup>554</sup> Thus, for patients on warfarin requiring reversal within 24 hours of surgery, IV vitamin K<sub>1</sub> (1–2.5 mg slowly) is recommended. INR assessment should be repeated prior to surgery to determine the need for supplemental plasma. For patients requiring reversal within 48 hours of surgery, 2.5 mg of oral vitamin K<sub>1</sub> can be given. In these cases, INR measurements should be repeated at 24 and 48 hours to determine the need for additional vitamin K or plasma.

Patients with serious or life-threatening bleeding require 10 mg of IV vitamin K<sub>1</sub> and 4-factor PCC.<sup>549,555,556</sup> Close monitoring of INR is required. If 4-factor PCC is unavailable, or the patient is allergic to heparin or had experienced HIT within 1 year, 3-factor PCC without heparin may be used.<sup>557</sup> Other alternatives if PCC is unavailable include fresh frozen plasma (FFP) and rhFVIIa.<sup>549,558</sup> There is a small risk for anaphylaxis (~1 in 3000 doses) associated with the IV administration of vitamin K<sub>1</sub>, especially when it is administered more rapidly than 1 mg per minute.<sup>559</sup> PCC, rhFVIIa, and plasma have been associated with a low risk for thromboembolic events<sup>560-562</sup> (see *Reversal of Anticoagulation* in the algorithm).

### Perioperative Management of Anticoagulation and Antithrombotic Therapy

Management of surgery-associated bleeding in patients with cancer is complicated by the need for anticoagulation in many of these patients due to their malignancy, cancer therapy, and/or comorbidities. It was shown in a large prospective study that patients with cancer chronically anticoagulated for VTE experienced higher rates of both periprocedural VTE (2% vs. 0.16%;  $P = .02$ ) and major bleeding (3.7% vs. 0.6%;  $P < .001$ ) compared to patients with cancer not chronically anticoagulated for VTE.<sup>563</sup> Another retrospective study found a high 30-day rate of VTE and major bleeding, both 4.1%, in patients with cancer-associated VTE requiring interruption of anticoagulation perioperatively.<sup>564</sup> Therefore, a balance of the thrombotic risk and bleeding risk is important.

In the case of emergent surgery, anticoagulation should be reversed (see *Reversal of Anticoagulation* in the algorithm). The timing of reinitiation of anticoagulation after surgery is influenced by the bleeding risk of the procedure and thrombotic risk factors of the individual (see *Bleeding Risk Assessment*, *Thromboembolic Risk Assessment for Arterial*



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*Thromboembolism and VTE, and Perioperative Management of Anticoagulation in Patients with Cancer* in the algorithm).

If the surgical procedure is non-emergent, an assessment of the bleeding risk should be performed before the procedure (see *Bleeding Risk Assessment* in the algorithm). For procedures associated with a very low risk of bleeding, including but not limited to minor dermatologic procedures, joint or soft tissue injections, GI endoscopy without biopsy or polypectomy, and minor dental procedures, anticoagulation can continue leading up to surgery.<sup>414</sup> Use of local hemostatic agents, such as topical tranexamic acid, aminocaproic acid, or thrombin-soaked absorbable gelatin powder, is encouraged in the event of bleeding during minor dental procedures. Patients at low, moderate, and high bleeding risk should undergo thromboembolic risk assessment (see *Table 2: Thromboembolic Risk Categories* in the algorithm). Based on these results, patients at low thromboembolic risk should stop anticoagulation without bridging therapy.<sup>414,565,566</sup> Of note, it is preferable to continue warfarin without discontinuation for some low-risk procedures, such as pacemaker or automatic implantable cardioverter defibrillator placement.<sup>414</sup> Patients at moderate or high thromboembolic risk should stop anticoagulation and bridging therapy should be considered.<sup>414</sup> Bridging anticoagulation therapy refers to the use of short-acting anticoagulants (LMWH or UFH) for 10 to 20 days during the periprocedural period.<sup>567</sup> However, in most circumstances bridging anticoagulation is not necessary for those taking DOACs, as the duration of interruption is shorter than with warfarin.<sup>566</sup> See *Table 3: Perioperative Management of Oral Anticoagulants: Hold Times* and *Table 4: Perioperative Management of Parenteral Anticoagulants: Hold Times* in the algorithm for specific recommendations on recommended hold times for DOACs, warfarin, and LMWHs.

Postoperative anticoagulation based on bleeding risk and thromboembolic risk should ensue after surgery. All patients should receive standard VTE

thromboprophylaxis once hemostasis is adequate (generally within 12–24 hours postoperatively), and thromboprophylaxis can be continued until therapeutic dose anticoagulation is resumed.<sup>414,566,568</sup> See the section on *Post-Procedural Resumption of Anticoagulation* in the algorithm for recommended timing of resumption for DOACs, warfarin, and LMWHs based on procedural bleeding risk. An IVC filter (retrievable filter preferred) should be considered if VTE (eg, lower-extremity DVT with or without PE) occurred within 1 month of planned surgery. Patients should be assessed periodically for filter retrieval once anticoagulation is safely resumed.

Bleeding risk can be attributed to both procedural and patient-specific factors. Providing a risk stratification system for surgeries and procedures in the context of perioperative antithrombotic drug use is challenging due to limited evidence.<sup>567</sup> However, several guidelines have classified higher-bleeding-risk surgeries and procedures to include GI procedures, percutaneous coronary interventions, neuraxial anesthesia and other neurosurgical procedures, and major orthopedic surgeries, among others. Dental procedures, cutaneous procedures, and selected cardiac procedures such as cardiac implantable devices and endovascular procedures and catheter ablation are considered operations with lower-bleeding risk<sup>414,569-572</sup> (for an exhaustive list of estimated bleeding risk for various surgical procedures, see *Bleeding Risk Assessment* in the algorithm). In terms of patient-specific factors, several scoring systems have been developed, such as the HAS-BLED score,<sup>573,574</sup> the ORBIT bleeding risk score,<sup>575</sup> and the biomarker-based ABC-bleeding risk score<sup>576</sup>; however, these scores have not been prospectively validated in the perioperative setting, particularly among patients with cancer.

In terms of thromboembolic risk assessment,<sup>414</sup> it must be noted that event rates per risk category may be higher in patients with cancer. Cancers associated with high thrombotic risk include pancreatic, liver, biliary, lung, stomach, brain, and esophageal cancers.<sup>2</sup> Additionally, the CHADS2 and



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CHADS2Vasc scoring systems were developed for patients with atrial fibrillation without cancer and may not be valid in patients with cancer.<sup>577,578</sup> Patients with atrial fibrillation may have additional risk factors for arterial thrombosis, including stroke or transient ischemic attack within 3 months and rheumatic heart valve disease.<sup>414,566</sup> The perioperative risk of recurrent thromboembolism in patients with VTE is influenced by the time of their thrombotic event (<3 months, within 3–12 months, >12 months) and the presence of thrombophilia, including: deficiencies in protein C, protein S, or antithrombin; gene mutations in factor V Leiden or prothrombin; or APS<sup>414</sup> (see the section on *Thromboembolic Risk Assessment for Arterial Thromboembolism and VTE* in the algorithm). The impact of these risk factors on the overall thromboembolic risk category should be assessed on a case-by-case basis in patients with cancer.

Overall, these Guidelines are meant to supplement but should not supersede clinical judgment. Careful attention to each individual's clinical situation is the best guide to management. For guidance on specific anticoagulation (warfarin, apixaban, dabigatran, edoxaban, fondaparinux, and rivaroxaban), see *Perioperative Management of Anticoagulation in Patients with Cancer* in the algorithm.

This section is based upon the Panel's assessment of the current literature on perioperative anticoagulation management in patients with cancer. There were considerable differences of opinions on management in many areas, which reflects the limited information on perioperative outcomes in patients with cancer on anticoagulation, who are likely to be at higher bleeding and thrombotic risk compared to patients without cancer. Since the risk of perioperative bleeding or thrombosis can be influenced by a large number of variables, including but not limited to the patient's cancer site and stage, proposed invasive procedure, antithrombotic medications, and concurrent medical conditions, periprocedural anticoagulation management should be determined on a case-by-case basis. For optimal

outcomes, it is essential to develop a perioperative anticoagulation plan in advance in conjunction with the patient's proceduralist.

### Heparin-Induced Thrombocytopenia

#### Evaluation

HIT is caused by a relatively common immunologic reaction to heparin-based products.<sup>415,579</sup> In a surveillance study, the incidence of HIT was 0.2% for all patients receiving heparin therapy and 1.2% in those exposed to heparin for >4 days.<sup>580</sup> HIT is triggered when UFH or LMWH binds to platelet factor 4 (PF4) and forms an immunogenic PF4-heparin complex.<sup>415,581</sup> The end result is a consumptive thrombocytopenia and profound prothrombotic state that triggers symptomatic thromboembolism in as many as 75% of patients.<sup>415,581</sup> Results of some studies indicate that the frequency of HIT with LMWH and UFH is similar,<sup>582,583</sup> whereas other studies suggest a lower incidence of HIT in patients receiving LMWH.<sup>584-587</sup> There is some evidence that patients with cancer are at increased risk of developing HIT and HIT-related VTE,<sup>588,589</sup> although this has not been firmly established. It has been suggested that factors such as anticoagulant dose and whether the patient is treated in the medical or surgical setting may account for these conflicting results, since a lower relative incidence of HIT with LMWH was observed for patients treated in the surgical setting receiving prophylactic doses of anticoagulant therapy.<sup>590</sup>

Clinical evidence of HIT includes development of thrombocytopenia, formation of necrotic lesions at injection sites, arterial thromboembolic complications, and/or development of VTE.<sup>591,592</sup> Most commonly, HIT occurs 5 to 10 days following initial exposure to heparin-based products. Rapid-onset HIT can occur within 1 day following administration of heparin in a patient with previous exposure to such agents within a period of 100 days.<sup>415,583</sup> Delayed-onset HIT is less common, and can occur days or weeks after heparin therapy has been discontinued.<sup>581</sup> A diagnosis of HIT

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is based on both clinical and serologic evidence.<sup>415</sup> The presence of both clinical sequelae of HIT, including thrombosis and thrombocytopenia (defined as a drop in platelet count by >50%) and anti-PF4/heparin antibodies, are needed for a diagnosis. Since most HIT antibodies do not activate platelets, a negative test result is more useful for excluding the diagnosis than a positive test result is for confirming it.<sup>593</sup> The specificity of functional platelet activation assays, such as the serotonin release assay (SRA), is higher than antigen assays, such as the heparin-PF4 ELISA, which detects the presence of HIT antibodies but does not assess their ability to activate platelets.<sup>415</sup> The diagnosis of HIT is complicated by the high frequency of heparin use in hospitals, possible delays in obtaining serologic test results, and other causes of thrombocytopenia in patients receiving heparin-based products. In addition, there are increased bleeding risks associated with substitution of a DTI for heparin. Therefore, it is critically important that a high level of clinical suspicion is present before a patient is treated for HIT.<sup>593</sup>

The 4T score is a simple, validated tool designed to assess the probability of HIT based on specific characteristics of four clinical parameters: thrombocytopenia, the timing of the onset of platelet fall, the presence of thrombosis or other clinical sequelae, and evidence of other potential causes of thrombocytopenia (see *HIT Pre-test Probability Score Assessment Tool* in the algorithm).<sup>594-596</sup> Evidence suggests that the negative predictive value of this assessment tool is considerably higher than its positive predictive value; hence, this tool is more likely to be useful in identifying patients at low risk for HIT.<sup>595,597</sup> Cuker and colleagues developed an alternative pre-test probability model based on broad expert opinion of HIT diagnosis known as the HIT Expert Probability (HEP) score. In a validation patient cohort, the HEP score demonstrated greater interobserver reliability and correlation with laboratory test results and expert assessment of the probability of HIT diagnosis than the 4T score.<sup>598</sup> It has been suggested that while the HEP and 4T scores are excellent

screening pretest probability models for HIT,<sup>599</sup> the HEP score might be superior to the 4T score among less experienced physicians and in patients in the intensive care unit (ICU).<sup>600</sup> For patients who develop suspected HIT after cardiac surgery, the cardiopulmonary bypass (CPB) score should be considered for risk assessment.<sup>601</sup> The CPB score was superior to the 4T score and the HEP score for identification of HIT in patients following cardiac surgery in a recent retrospective study.<sup>602</sup> The 4T score has not been validated in patients with cancer and may have less utility in this population, particularly in patients receiving chemotherapy who have alternative causes for thrombocytopenia.<sup>603</sup>

The Panel recommends evaluation using any of the above scoring systems if HIT is suspected (see *HIT Pre-test Probability Models* in the algorithm). For patients classified with low HIT probability, options include: continue UFH/LMWH, consider alternative causes of thrombocytopenia, monitor clinical status, and consider HIT antibody testing by ELISA in select patients. In the case of a negative ELISA test (estimated HIT probability 0%<sup>604,605</sup>), patients should continue UFH/LMWH and be monitored for clinical status. Based on clinical judgment, initiation of argatroban, bivalirudin, or fondaparinux in place of UFH/LMWH may be warranted in select patients. In the case of a positive ELISA test (estimated HIT probability 1.5%<sup>604,605</sup>), the Panel recommends SRA or P-selectin expression assay (PEA) testing and reassessment of risks and benefits of UFH/LMWH versus alternative non-heparin anticoagulant. In the case of a positive SRA/PEA test, the patients should be treated for HIT. In the case of a negative SRA/PEA test, HIT diagnosis and other causes of thrombocytopenia should be reconsidered, and the use of UFH/LMWH can resume.

Patients classified as having an intermediate/high probability of HIT should initially be treated as having a diagnosis of HIT while awaiting confirmatory ELISA test results. UFH/LMWH exposure should be eliminated from all





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sources (ie, treatment, prophylaxis, line flushes, coated catheters). Warfarin should be discontinued and reversed with vitamin K. Alternative non-heparin anticoagulant should be started. For patients without an indication for therapeutic anticoagulation who are judged to be at high risk of bleeding and moderate risk of HIT, a prophylactic dose of a non-heparin anticoagulant may be considered while awaiting the results of initial testing.<sup>39</sup> Platelet transfusions should be avoided unless the patient is actively bleeding or is at high risk of bleeding. In the case of a negative ELISA test and intermediate 4T score (estimated HIT probability 0.6%<sup>604,605</sup>), HIT diagnosis and other causes of thrombocytopenia should be reconsidered, and the use of UFH/LMWH can resume. In the case of a negative ELISA test and high 4T/HEP/CPB score (estimated HIT probability 6.6%<sup>604,605</sup>), the Panel recommends continuation of alternative non-heparin anticoagulant and repeat ELISA/SRA/PEA test. Institution-specific ELISA optical density value thresholds should be considered when determining whether to send for SRA/PEA testing. In the event of a positive test result, the patient should be treated for HIT. A negative repeat ELISA/SRA/PEA test result warrants reconsideration of HIT diagnosis and other causes of thrombocytopenia, as well as resumption of UFH/LMWH. In the case of a positive ELISA test and intermediate or high 4T score (estimated HIT probability 54%–93%, respectively<sup>604,605</sup>), or high HEP/CPB score, the patient should be treated for HIT (see *Treatment for HIT* in the algorithm).

### Anticoagulants for the Treatment of HIT

#### Direct Thrombin Inhibitors

Argatroban is approved by the FDA for the immediate treatment of HIT.<sup>606</sup> Argatroban is primarily metabolized by the liver, and prolonged clearance of this agent has been seen in patients with hepatic insufficiency.<sup>606</sup> Thus, its use should be avoided in patients with hepatic failure. The manufacturer-recommended dose for argatroban, similar to that of many anticoagulants, may be too high for the treatment of HIT in patients who

are critically ill, and thus should be lowered.<sup>607-609</sup> In a prospective randomized trial, argatroban significantly reduced the combined endpoint of death, limb amputation, and occurrence of new thrombotic events among patients with HIT without thrombosis compared with historical controls (25.6% vs. 38.8%;  $P = .014$ ). No significant differences in the combined endpoint were noted with argatroban versus control among patients with HIT and thrombosis.<sup>610</sup> Similarly, results from the second trial of argatroban showed significantly decreased incidence of the combined endpoint with argatroban compared with historical controls in patients with HIT without thrombosis (28.0% vs. 38.8%;  $P = .04$ ), but not in patients with HIT and thrombosis (41.5% vs. 56.5%;  $P = .07$ ).<sup>611</sup> In both trials, argatroban was shown to significantly decrease the incidence of death due to thrombosis, as well as the incidence of new thrombosis compared with controls ( $P < .05$ ), regardless of concurrent thrombosis status.<sup>610,611</sup>

Bivalirudin is another DTI recommended for the off-label treatment of HIT. Similar to argatroban, dose reductions are suggested for bivalirudin in patients with HIT and hepatic and/or renal insufficiency or critical illness.<sup>612,613</sup> Besides smaller retrospective studies,<sup>612,613</sup> data regarding bivalirudin use in HIT are limited. The largest retrospective study of bivalirudin included 386 patients with suspected or confirmed HIT. Of these, 57.8% had thrombosis at HIT diagnosis and 4.6% developed new thrombosis while on bivalirudin. Major bleeding occurred in 7.6% of patients, with a significant increase in the population with critical illness (13.1%; OR, 2.4; 95% CI, 1.2–4.9;  $P = .014$ ); the 30-day all-cause mortality rate was 14.5% with 1.7% of deaths being HIT-related.<sup>614</sup> It is important to note that bivalirudin has been associated with anaphylaxis. Overall, no head-to-head trials comparing different DTIs in the treatment of HIT have been published. Clinician experience and comfort level with the agents used should be a consideration in the choice of therapy.





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### **Indirect Factor Xa Inhibitor**

Fondaparinux is a recommended alternative to parenteral DTIs in HIT treatment. There have been rare reports of fondaparinux use and development of HIT, although in most cases patients had prior exposure to UFH or LMWH.<sup>615-618</sup> Thus, the NCCN Panel recommends fondaparinux as a second-line agent. The two largest retrospective studies demonstrating fondaparinux safety and efficacy for HIT treatment enrolled 84 and 133 patients, respectively.<sup>619,620</sup> In the first study, thrombosis and bleeding occurred in 16.5% and 21.1% of patients in the fondaparinux group, compared with 21.4% and 20% in the control group (treated with argatroban or danaparoid).<sup>620</sup> In the second study, HIT-specific complications and all-cause in-hospital mortality occurred in 0% of patients in the fondaparinux group, compared with 11.7% and 6.3% of patients treated with argatroban, lepirudin, or danaparoid.<sup>619</sup> Fondaparinux has also been used in case reports and smaller studies for patients with HIT and generally appears to be safe.<sup>621-624</sup> Use of a DTI should be considered instead of fondaparinux if the CrCl is between 30 to 50 mL/min and fondaparinux should be avoided in patients with a CrCl <30 mL/min.

### **Direct Oral Anticoagulants**

Apixaban, rivaroxaban, dabigatran, and edoxaban are rarely used for the initial treatment of HIT; however, they may be a reasonable option for patients who have stabilized on initial treatment for HIT using a DTI or fondaparinux, have no procedures planned, and have no contraindications. The use of apixaban<sup>625-631</sup> and dabigatran<sup>631-634</sup> for HIT treatment is limited to case reports and small retrospective studies that included very small numbers of patients with cancer. The most evidence supporting the use of DOACs is with rivaroxaban, which includes case reports, a systematic review, and a small prospective study.<sup>630,631,635-643</sup> In the systematic review, a thrombosis rate of 1 of 46 patients (2.2%; 95% CI, 0.4%–11.3%) and no major hemorrhage were reported in patients treated with rivaroxaban during acute HIT; similar results were reported for

apixaban and dabigatran.<sup>643</sup> The only literature report on the use of edoxaban for HIT treatment is a case study of one patient who underwent surgery for esophageal cancer.<sup>644</sup>

### **Warfarin**

The Panel recommends that warfarin should not be initiated in patients with HIT until after platelet count recovery because of the potential for skin necrosis and/or venous gangrene.<sup>415,645</sup> After platelet recovery, warfarin should be overlapped with a DTI or fondaparinux for at least 5 days; the DTI or fondaparinux should be discontinued only after the INR has reached the intended target range (INR 2–3) for 24 hours. Since both DTIs and warfarin reduce thrombin activity, coadministration of a DTI and warfarin produces a combined effect on laboratory measurements of both aPTT and INR. However, concurrent therapy, compared with warfarin monotherapy, exerts no additional effect on vitamin K-dependent factor X activity. Therefore, the anticoagulation impact of warfarin may be underestimated in the presence of a DTI. DTIs can prolong the INR during co-therapy with warfarin. Since argatroban has the lowest affinity for thrombin of the two DTIs, higher molar plasma concentrations of argatroban are needed to prolong the aPTT; hence, prolongation of INR is more pronounced with argatroban compared with the other DTIs.<sup>646,647</sup> A higher target INR should therefore be achieved before argatroban is discontinued.<sup>415,606,647</sup> Once the DTI is discontinued, a repeat INR and aPTT should be obtained 2 to 6 hours later to determine whether the INR is therapeutic on warfarin monotherapy. Alternatively, chromogenic factor X levels (which are not affected by DTIs) can be used to monitor warfarin activity during transition from co-therapy with argatroban.<sup>648,649</sup>

### **Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) works by inhibiting HIT antibody-induced platelet activation.<sup>650,651</sup> Good to excellent responses have been observed with IVIG across 36 cases, with most of these cases involving

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patients with autoimmune HIT, which includes a subset of patients whose antibodies activate platelets both in the presence and absence of heparin.<sup>650</sup> Use of IVIG is typically adjunct to alternative anticoagulation in these studies. Thrombosis is a critical adverse event for patients treated with IVIG; however, to date, evidence demonstrating prothrombotic effects of this treatment is lacking.<sup>650</sup> While studies still remain limited, the Panel currently recommends use of IVIG in patients with autoimmune HIT as well as in persisting (also known as refractory) HIT, which is an autoimmune HIT disorder. The Panel also notes that IVIG may be useful in patients with HIT who are at high risk of bleeding.

### ***Platelet Transfusions***

As noted above, platelet transfusions should be avoided unless the patient is actively bleeding or is at high risk of bleeding.

### **Patient Resources for VTE Management**

- National Blood Clot Alliance - [www.stopthecлот.org](http://www.stopthecлот.org)
- ClotCare Online Resource - <http://www.clotcare.com/>
- North American Thrombosis Forum - <http://natfonline.org/patients>

### **Summary**

The NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease provide a framework on which to prevent, diagnose, and treat VTE in adult patients with cancer. The recommendations and corresponding clinical data discussed here aid in the identification of patients with cancer at high risk for the development of VTE, suggest prophylactic regimens for these patients that can mitigate this common yet life-threatening complication, and provide guidance on the management and treatment strategies for the diverse subtypes of VTE should they develop. Application of these recommendations will help achieve optimal

yet safe outcomes for patients with malignancy who are at high risk of developing or who have already developed VTE.



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