National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer-Associated Venous Thromboembolic Disease

NCCN.org

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National Comprehensive Cancer Network®

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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN Member Institutions, click here: https://www.nccn.org/clinical_trials/member_institutions.aspx

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2020 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2019 include:

General

- **Venous Thromboembolism (VTE) Prophylaxis: Global**
  - **Several sections of content have been moved, rearranged, consolidated, and renamed. The TOC page and links to other pages of the Guidelines have been updated to reflect these changes in the algorithm.**
- **Heparin-Induced Thrombocytopenia (HIT) recommendations have been moved to the end of the Guidelines.**

VTE-1

Workup

- **6th bullet was added: *VTE risk assessment***
- **New footnotes b and g were added:**
  - ***The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all hospitalized cancer patients. Although multiple risk assessment models (RAMs) have been developed for hospitalized medical and surgical patients, none of these RAMs have been validated in prospective management studies conducted in hospitalized cancer patients.***
  - ***Results from a randomized trial (including a limited number of patients with cancer) suggest that addition of mechanical prophylaxis to pharmacologic prophylaxis in critically ill patients may not reduce the incidence of DVT. (Arabi YM, et al. N Engl J Med 2019;380:1305-1315.)***
- **Footnote c was modified: See Contraindications to ~~Prophylactic or Therapeutic Anticoagulation Treatment~~ *VTE Prophylaxis* (VTE-B). ~~See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-C)~~.**

VTE-2

At-Risk Population:

- **6th bullet was modified: "Providers are encouraged to discuss VTE risk factors, *bleeding risk factors,* risks and benefits of VTE prevention..."**
- **The Surgical oncology patient pathway now leads the reader to: ~~See Inpatient/Outpatient Prophylactic Anticoagulation Treatment (VTE-D)~~ *See Prophylactic Anticoagulation Options for Surgical Oncology Outpatients (VTE-C)***
- **The Medical oncology patient pathway was significantly modified:**
  - **Multiple myeloma patients receiving ~~thalidomide, lenalidomide, or pomalidomide:~~ *immunomodulatory drugs (IMiDs)* (change to "IMiDs" applied globally)**
    - ◊ **~~High risk: Recommend anticoagulant VTE prophylaxis~~**
    - ◊ **~~Low risk: Recommend aspirin~~**
    - ◊ ***See VTE Risk Assessment Models and Prophylaxis based on SAVED (VTE-3) and IMPEDE VTE (VTE-4) Scores***
  - ~~**Other outpatient settings**~~ ***Other cancer patients: VTE risk evaluation based on Khorana score (See VTE-D)***
    - ◊ ~~**No routine VTE prophylaxis recommended outside of a clinical trial setting**~~ ***Intermediate or high risk for VTE (Khorana score ≥2)***
      - – ***Consider oral anticoagulant prophylaxis for up to 6 months***
        - ▪ ***Apixaban 2.5 mg PO BID***
        - ▪ ***Rivaroxaban 10 mg PO QD***
    - ◊ ***Low risk for VTE (Khorana score <2)***
      - – ***No routine VTE prophylaxis***
- **Footnote c was added to this page: See Contraindications to VTE Prophylaxis (VTE-B).**
- **New footnote i was added: *For agent-specific contraindications, see Anticoagulant Options: Contraindications and Warnings (VTE-E, 3 of 4).***
- **A footnote was removed: Multiple myeloma patients receiving thalidomide/lenalidomide/pomalidomide: in combination with high-dose dexamethasone (≥480 mg per month) or doxorubicin or multi-agent chemotherapy or for myeloma patients with 2 or more individual or myeloma risk factors (See VTE Risk Factors in Patient with Cancer [VTE-A 2 of 3]), recommended prophylaxis is LMWH (enoxaparin 40 mg subcutaneous every 24 hours or its equivalent) or warfarin (adjusted to international normalized ratio [INR] 2-3). For low-risk myeloma patients with one or fewer individual or myeloma risk factors, aspirin 81–325 mg daily may be used. Aspirin should not be used in non-myeloma patients for VTE prevention.**

VTE-3 and VTE-4 were added: *VTE Risk Assessment Models and Prophylaxis in Patients with Multiple Myeloma Receiving IMiDs*

- **These two pages are replacing VTE-A, 2 of 3, which has been removed in this version of the guidelines.**

VTE-A (formerly VTE-A 1 of 3)

- **Treatment-related risk factors**
  - **3rd bullet, 2nd sub-bullet was added: *Proteasome inhibitors***

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Updates in Version 1.2020 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2019 include:

VTE-B: This page was extensively revised and split into 2 new pages: New VTE-B "*Contraindications to VTE Prophylaxis*" and New VTE-F "*Contraindications to Therapeutic Anticoagulation*"

- **Contraindications to Prophylactic ~~or Therapeutic~~ Anticoagulation ~~Treatment~~**
  - **1st bullet was modified: Active bleeding ~~(major): more than 2 units transfused in 24 hours~~**
  - **2nd bullet was modified: Thrombocytopenia (platelets <*30,000*–50,000/mcL *or clinical judgment*) (also modified on VTE-F)**
  - **3rd bullet was modified: 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)* (also modified on VTE-F)**
  - **4th bullet was added: *Indwelling neuraxial catheters (contraindication for apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban, or enoxaparin dose exceeding 40 mg daily)***

VTE-C (formerly VTE-D)

- **This page was extensively revised and renamed: ~~Inpatient/Outpatient Prophylactic Anticoagulation Treatment~~ *Prophylactic Anticoagulation Options for Inpatients and Surgical Oncology Outpatients***

VTE-D (formerly VTE-A, 3 of 3)

- **The title was modified: VTE Risk ~~Factors~~ *Assessment* in Cancer Outpatients**

SVT-1

- **SVT Treatment for Forearm (top pathway):**
  - **If peripheral catheter related, remove catheter**
    - **2nd sentence was modified: If progression *symptomatically or on imaging*, consider anticagulation**
- **Footnote c was modified: ~~Anticoagulation for SVT should be administered using therapeutic dosing.~~ *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 cancer patients (Beyer-Westendorf J, al. Lancet Haematol 2017;4:e105-e113). Therapeutic dosing may be used at the clinician's discretion.* See Therapeutic Anticoagulation for Venous Thromboembolism (VTE-E).**

DVT-1

- **Workup/Imaging**
  - **3rd bullet was modified for both the "Clinical suspicion of DVT" and "Incidental DVT" pathways:**
    - **PT, aPTT ± *fibrinogen***

DVT-2

- **DVT: Treatment**
  - **Recommendation for patients who have a DVT in the Calf with a Contraindication to anticoagulation (middle pathway), was revised: Follow-up ~~in 1 week with duplex US~~ *with serial US* ("duplex US" was replaced by "US" throughout the guideline)**

PE-1

- **Evaluation**
  - **"EKG" was changed to "ECG" in both the "Clinical suspicion of PE" and "Incidental PE" pathways**

PE-2

- **PE: Treatment**
  - **Recommendation for patients who do not have a Contraindication to anticoagulation (top pathway), was revised: Upon diagnosis, PE patients should be considered for risk stratification *with one or more tools to identify high-risk patients***
- **Footnote g was modified: ~~Consider IVC filter (retrievable filter preferred) in the presence of a proximal lower extremity or pelvic DVT.~~ *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).***

SPVT-1

- **Clinical suspicion of SPVT**
  - **12th bullet was removed: Lower extremity edema**
- **Footnote a, 5th bullet was removed: Thrombophilia**

VTE-E: Therapeutic Anticoagulation for Venous Thromboembolism

- **This section was extensively revised, rearranged, reformatted, and condensed.**

VTE-E, 1 of 4

- ***General Guidelines***
  - **1st bullet, a sub-bullet and 4 sub-sub bullets were moved to this page (previously on VTE-E, 3 of 5):**
    - **Duration of Anticoagulation as Recommended by Guideline:**
      - **1st sub-sub bullet was modified: ~~Minimum time of 3 months~~ *At least 3 months or as long as active cancer or cancer therapy***
      - **3rd sub-sub-bullet was modified: For catheter-associated thrombosis, anticoagulate as long as catheter is in place. ~~Recommended total duration of therapy is at least 3 months.~~**

Continued

Updates in Version 1.2020 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2019 include:

VTE-E, 1 of 4 (Continued)

- 2nd bullet was modified: Select regimen based on *these factors (not in order of importance)*: Renal failure (creatinine clearance [CrCl] <30 mL/min), *hepatic disease (elevated transaminases or bilirubin, Child-Pugh B and C liver impairment, or cirrhosis),* inpatient/outpatient, FDA approval, cost, *patient preference,* ease of administration, monitoring, bleeding risk assessment, and ability to reverse anticoagulation. See Contraindications and Warnings on ~~VTE-E, 4 of 5~~ *VTE-E, 3 of 4*.

VTE-E, 2 of 4

- *DOACs (preferred for patients without gastric or gastroesophageal lesions)*
  - Apixaban *(category 1)*
    - ◊ 10 mg ~~orally~~ *PO* BID for 7 days ~~then~~ *followed by* 5 mg *PO* BID ("then" was replaced by "followed by" and route of administration was added for all agents throughout this section for clarity)
  - Edoxaban *(category 1)*
    - ◊ Initial therapy with LMWH or UFH 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 inhibitors ~~or inducers~~)
- LMWH *(preferred for patients with gastric or gastroesophageal lesions)*
  - Dalteparin (category 1)
    - ◊ 200 units/kg SC daily for 30 days, then *switch to* 150 units/kg once daily
  - Enoxaparin
    - ◊ 1 mg/kg SC every 12 hours *(can consider decreasing intensity to 1.5 mg/kg daily after first month)*
- *DOACs (if above regimens not appropriate or unavailable)*
  - Dabigatran
    - ◊ Initial therapy with LMWH or UFH for at least 5 days *followed by* dabigatran 150 mg PO BID
- Apixaban and dabigatran recommendations are no longer limited to "patients who refuse or have compelling reasons to avoid LMWH"
- UFH (category 2B)
  - IV 80 units/kg ~~load~~ *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 *BID* (category 2B) (these same changes were made to the UFH + warfarin recommendations; "load" was changed to "bolus" throughout this section)
- Warfarin
  - 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)*
  - LMWH + warfarin options:
    - ◊ Dalteparin 200 units/kg SC daily *or 100 units/kg SC every 12 hours*
- Footnote a was added: *Patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with direct oral anticoagulants (DOACs).*
- Footnote d was modified: 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.
- Footnote g was modified: "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 ≥2 ~~for 24 hours~~..."

VTE-E, 3 of 4

- Footnote h was modified: Although stage IV chronic kidney disease is not listed as a contraindication in the FDA-approved label for apixaban, the NCCN Panel ~~avers~~ *acknowledges* that there are insufficient data to support safe apixaban dosing in these patients, especially those who are on hemodialysis.

VTE-E, 4 of 4

- A reference was updated: Prescribing Information: Dabigatran etexilate mesylate capsules, for oral use; ~~2017~~ *2019*. Available at: ~~https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s028lbl.pdf.~~ *https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020287s072lbl.pdf*.
- 3 references were added:
  - *McBane RD, 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost 2020;18:411-421.*
  - *Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019;380:711-719.*
  - *Kraaijpoel N, Di Nisio M, Mulder FI, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: Results from the Hokusai VTE Cancer Study. Thromb Haemost 2018;118:1439-1449.*

Continued

Updates in Version 1.2020 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2019 include:

VTE-F (New Contraindications to Therapeutic Anticoagulation page; this information was formerly on VTE-B)

- Absolute *contraindications*
  - 1st sub-bullet was modified: Active bleeding (major): ~~more than 2 units transfused in 24 hours~~
  - 2nd sub-bullet was added: *Indwelling neuraxial catheters*
  - 3rd and 4th sub-bullets were moved to "Absolute *contraindications*" (previously under "Relative *contraindications*"):
    - Neuraxial anesthesia/lumbar puncture
    - Interventional spine and pain procedures
  - A sub-bullet was removed: Recent central nervous system (CNS) bleed, hemorrhagic CNS metastases
- Relative *contraindications*
  - 4th sub-bullet was modified:
    - Severe platelet dysfunction ~~(uremia, medications, dysplastic hematopoiesis)~~
- Footnotes 1 and 2 were added:
  - *For agent-specific contraindications, see VTE-E, 3 of 4.*
  - *Active bleeding with >2 units transfused, decrease in hemoglobin by ≥2 g/dL, or intracranial or intraspinal bleeding.*
- Footnote 7 was modified: 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.

VTE-G (formerly VTE-C)

- 5th bullet was added: *When using apixaban, edoxaban, or rivaroxaban in the setting of thrombocytopenia, hold until platelet count recovers to >50,000/mcL.*

VTE-H (This section has been refomatted into a table and condensed into 1 page)

- *Anticoagulation agent:* UFH
  - Check
    - *UFH anti-factor Xa levels*
  - Results
    - Therapeutic aPTT/*UFH anti-factor Xa level*
      - *Action*
        - 3rd bullet was modified: Increase dose of UFH or switch to one of the following: LMWH, ~~or~~ fondaparinux, *or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)*
    - Sub-therapeutic aPTT/*UFH anti-factor Xa level*
      - *Action*
        - 2nd bullet was added: *Consider alternative anticoagulant*
- *Anticoagulation agent:* LMWH
  - Action
    - 2nd bullet was modified: Move to every-12-hour schedule, or increase dose, or switch to fondaparinux *or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)*
- *Anticoagulation agent:* Fondaparinux
  - Action
    - 2nd bullet was modified: Switch to UFH, ~~or~~ LMWH, *or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)*
- *Anticoagulation agent:* Warfarin
  - Results
    - Therapeutic INR
      - *Action*
        - Bullet was modified: Switch to LMWH ~~(preferred)~~, UFH, ~~or~~ fondaparinux, *or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)*
    - Sub-therapeutic INR
      - *Action*
        - Bullet was modified: Increase warfarin dose and treat with parenteral agent until INR target achieved or consider switching to LMWH ~~(preferred)~~, UFH, ~~or~~ fondaparinux, *or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)*
- *Anticoagulation agent:* Apixaban, dabigatran, edoxaban, rivaroxaban
  - Action
    - 2nd bullet was added: *Switch to fondaparinux*
- Footnote 8 was modified: Although data are limited, doses are generally increased ~~by 25%~~ *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).*

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VTE-1

- 1st bullet, 2 sub-bullets were added and 3 sub-sub-bullets were added or modified:
  - *Pharmacomechanical devices*
    - ◊ *Alteplase 10 mg to 25 mg per session*
  - *Infusion catheters*
    - ◊ Alteplase ~~(tPA) 0.5–1.0 mg/h IV~~ *0.5 mg to 1 mg per hour for 12–24 hours*
    - ◊ Reteplase ~~0.25–0.75 units/h IV~~ *0.5 units to 1 units per hour for 12–24 hours*
- 2nd bullet
  - 1st sub-bullet was added: *Systemic thrombolysis*
    - ◊ 2 sub-sub bullets were modified:
      - – Alteplase ~~(tPA)~~ 100 mg IV over 2 hours
      - – Tenecteplase ~~0.25–0.5 mg/IV~~ (category 2B)
        - ▪ A tenecteplase dosing table was added
      - – A sub-sub bullet was added: *Alteplase 50 mg as a 10 mg bolus followed by 20 mg per hour for 2 hours*
  - 2nd sub-bullet, a sub-sub-bullet was added: *Alteplase 1 mg per hour per lung for 12–24 hours*
- Footnote 1 was modified: *A* post-procedural ~~x-ray venoram~~ *imaging study* is recommended to confirm *the* results of ~~catheter-directed~~ thrombolysis.
- Footnotes 2, 3, 4, 6 and 7 were added:
  - *Different FDA-approved catheters and devices exist to deliver thrombolytic agent 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.*
  - *Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017;377:2240-2252.*
  - *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.*
  - *Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-1411.*
  - *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.*
- Footnote 8 was modified: US-assisted catheter-directed thrombolysis ~~is a treatment option~~ *has been used* for PE ~~in~~ patients 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. ~~The panel recommends alteplase infusion at a rate of 1 mg/h per drug delivery catheter (2 mg/h for bilateral PE) with a total dose of 24 mg.~~ *Alteplase is administered at a rate of 1 mg/h per drug delivery catheter (2 mg/h for bilateral PE).* ~~The~~ *A*lteplase regimen is infused for 24 hours with one catheter and 12 hours for two catheters.
- A footnote was removed: Thrombolytic therapy for DVT is generally delivered by catheter-based techniques in conjunction with mechanical thrombectomy.

VTE-L, 1 of 8 (formerly VTE-F)

- 3rd bullet
  - A sub-bullet was added: *andexanet alfa*
  - A sub-bullet was removed: 3-factor prothrombin complex concentrate (3-factor PCC)
- Precautions/Additional Considerations (for Heparin)
  - 4th bullet was modified: Protamine reverses a variable amount of LMWH anti-Xa activity ~~(enoxaparin 54%, dalteparin 74%)~~.

VTE-L, 3 of 8

- Precautions/Additional Considerations (for Warfarin with Life-threatening bleeding)
  - 3rd bullet was modified: Administer 4-factor PCC IV push at a rate not exceeding 5 mL/min. 4-factor PCC is associated with thromboembolism ~~in 7.8% of patients~~ within 30 days of administration.
  - 5th bullet was modified: FFP is associated with thromboembolism ~~in 6.4%~~ within 30 days of administration.

VTE-L, 5 of 8

- Reversal of Antigoagulation (for Dabigatran)
  - 2nd bullet was modified: Adminster idarucizumab, ~~5 g IV~~ *2.5 g in 2 consecutive boluses*.
- Precautions/Additional Considerations (for Dabigatran)
  - 3rd bullet was modified: Idarucizumab is associated with thromboembolism ~~in 4.8% of patients~~ within 30 days.

Continued

Updates in Version 1.2020 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2019 include:

VTE-L, 6 of 8

- Reversal of Anticoagulation (for Rivaroxaban or Apixaban)
  - 2nd bullet, 2nd sub-bullet, 2nd sub-sub-bullet was modified and 3rd sub-sub-bullet was removed:
    - 4-factor PCC 25–50 units per kg (based on units of Factor IX per kg of actual body weight) *or fixed dose of 2,000 units*
    - ~~rhFVIIa 20–120 mcg/kg IV~~
- Precautions/Additional Considerations (for Rivaroxaban or Apixaban)
  - 2nd bullet was modified: Andexanet alfa is associated with thromboembolism ~~in 10% of patients~~ within 30 days of administration.

VTE-L, 7 of 8

- Table 1: Andexanet Alfa Dosing Strategy
  - *Last* Dose
    - Rivaroxaban ~~<~~ ≤10 mg
    - Apixaban ~~<~~ ≤ 5 mg
- 2 references were added:
  - *Dager WE, Roberts AJ, Nishijima DK. Effect of low and moderate dose FEIBA to reverse major bleeding in patients on direct oral coagulants. Thromb Res 2019;173:71-76.*
  - *Schulman S, Gross PL, Richie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: A prospective cohort study. Thromb Haemost 2018;118:842-851.*

PMA-1 (PMA-1 and PMA-2 were condensed into this one page)

Two column headers were added to the page: "*Bleeding Risk Assessment*" (moved from the Non-emergent surgery pathway to the header) and "*Thromboembolism (TE) Risk Assessment*"

- 1st bullet (end of Emergent surgery pathway) was modified: Postoperative anticoagulation *(PMA-C)* based on bleeding risk *(PMA-A) and TE risk (PMA-B)* (these changes were also made to step after Surgery in the Non-emergent surgery pathway)
- A recommendation was added to the Non-emergent surgery pathway: *Assess bleeding risk (PMA-A)*
  - The *Bleeding Risk Assessment* options were modified:
    - Very low *bleeding* risk
    - Low, High and Very high *bleeding* risk
  - The recommendation for the Low, High and Very high *bleeding* risk pathway was modified: ~~Perioperative thromboembolism risk assessment; See PMA-2;~~ *Assess TE risk (PMA-B)*
    - A recommendation that had been in the algorithm pathway was modified and added as a footnote: 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.*
    - *TE Risk Assessment* options and recommendations were modified:
      - Low *TE risk*
        - Stop anticoagulation without bridging therapy *(PMA-C)*
      - Moderate *or* High *TE risk* (these two pathways were condensed into one pathway)
        - Stop anticoagulation, consider bridging therapy *(PMA-C)*
- 3 footnotes were removed (replaced by links added to the algorithm)
  - See Table 1: Bleeding Risk Assessment (PMA-A).
  - See Table 3: Perioperative Anticoagulation Management Guideline (PMA-C).
  - See Table 2: Thromboembolic Risk Assessment for Arterial and Venous Thromboembolism (PMA-B).

PMA-A (PMA-A, 1 of 2 and PMA-A, 2 of 2 were condensed into this one page)

- Title of page was modified: Table 1: Bleeding Risk Assessment *Tables*
- Estimated Bleeding Risk of Various Surgical Procedures
  - Bleeding Risk Category: Low
    - "Pacemaker or automatic implantable cardioverter defibrillator (AICD) placement" was moved from High to Low Bleeding Risk Category
    - A Surgery or Procedure was modified: Central venous catheter *placement and* removal

PMA-B

- Title of page was modified: ~~Table 2:~~ Thromboembolic Risk Assessment for Arterial and Venous Thromboembolism

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Cancer-Associated Venous Thromboembolic Disease

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Updates in Version 1.2020 of the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease from Version 1.2019 include:

HIT-1

- Calculate HIT pre-test probability (4T Score): Low (4T Score <4) pathway
  - SRA negative pathway was modified to remove the recommendation to "Reassess HIT diagnosis and treatment with alternative non-heparin anticoagulant." This pathway now directs the reader to the pathway below, which has the following recommendations:
    - ◊ Reconsider diagnosis of HIT and other causes of thrombocytopenia
    - ◊ Consider resumption of UFH/LMWH
- A footnote was added: *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.)*

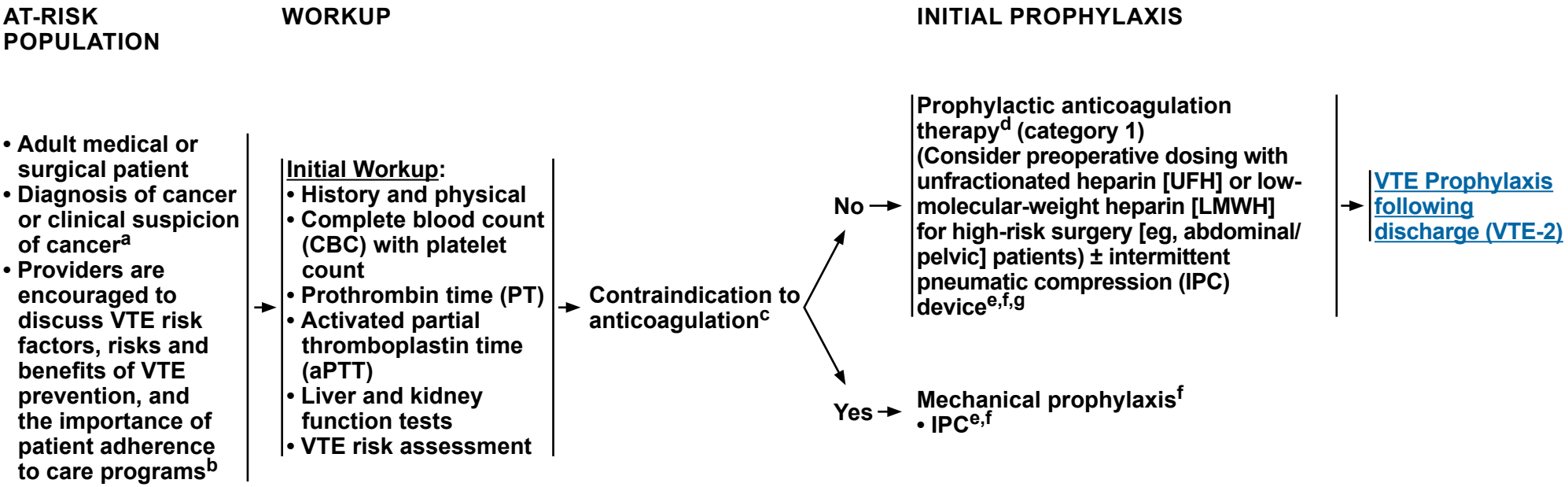
HIT-2

- A bullet was added: *Global assessment of bleeding and clotting should be performed prior to treatment.*
- Initial Treatment for Patients with Suspected or Confirmed HIT
  - 1st bullet, 3rd sub-bullet was added: *Full-dose anticoagulation is generally preferred, depending on assessment of bleed and clot risks.*
- Additional Recommendations for Patients with Confirmed HIT
  - 1st bullet was modified: ~~Consider four~~ *Lower*-extremity ~~duplex~~ US *is recommended* to identify asymptomatic DVT*; consider upper-extremity US based on clinical situation.*
  - 2nd bullet, a sub-bullet was added, a sub-bullet was modified, and the treatment options were re-ordered:
    - ◊ DOACs *(preferred)*: For patients with adequate renal and hepatic function and no other contraindications (listed on VTE-E, 2 of 4).
    - ◊ *Fondaparinux*
    - ◊ Warfarin

HIT-B

- This page was rearranged, and options were reordered based on Category of Evidence and Consensus, when appropriate.
- Direct Thrombin Inhibitors *(DTIs)*
  - 2nd bullet, 2nd sub-bullet, 5th sub-sub bullet was modified: Renal replacement therapy or combined hepatic/renal failure: Consider argatroban for isolated renal failure or use ~~0.03~~ *0.04* mg/kg/h
- Warfarin
  - 3rd and 4th bullets have changed order.
  - 6th bullet was modified: ~~Alternatively~~ *If available,* chromogenic factor X activity, which is not affected by DTIs, can be used to monitor warfarin during co-therapy.

INPATIENT VENOUS THROMBOEMBOLISM PROPHYLAXIS



[a] See VTE Risk Factors in Patients with Cancer (VTE-A).

[b] The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all hospitalized cancer patients. Although multiple risk assessment models (RAMs) have been developed for hospitalized medical and surgical patients, none of these RAMs have been validated in prospective management studies conducted in hospitalized cancer patients.

[c] See Contraindications to VTE Prophylaxis (VTE-B).

[d] Discuss VTE prevention and the risks/benefits of pharmacologic and mechanical VTE prophylaxis. A systematic approach to patient risk assessment is recommended. Institutions are strongly encouraged to implement best practice programs to monitor provider and patient adherence to VTE prophylaxis. See Prophylactic Anticoagulation for Inpatients and Surgical Oncology Outpatients (VTE-C).

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

[f] Most data come from surgical or stroke patients; this is an extrapolation to the medical population. See Contraindications to VTE Prophylaxis (VTE-B).

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

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VTE PROPHYLAXIS FOLLOWING DISCHARGE AND FOR AMBULATORY CANCER PATIENTS AT RISK[a]

AT-RISK POPULATION

- Adult medical or surgical patient
- Diagnosis of cancer
- Patient received VTE prophylaxis during hospitalization
- Cancer inpatient intended for discharge
- Outpatients at risk
- Providers are encouraged to discuss VTE risk factors, bleeding risk factors, risks and benefits of VTE prevention, and the importance of patient adherence to care programs

Surgical oncology patient → Out-of-hospital primary VTE prophylaxis is recommended for up to 4 weeks post-operation for high-risk abdominal or pelvic cancer surgery patients[h] → See Prophylactic Anticoagulation Options for Surgical Oncology Outpatients (VTE-C)

Medical oncology patient

- Multiple myeloma patients receiving immunomodulatory drugs (IMiDs) → See VTE Risk Assessment Models and Prophylaxis based on SAVED (VTE-3) and IMPEDE VTE (VTE-4) Scores
- Other cancer patients: VTE risk evaluation based on Khorana score (See VTE-D)
  - Intermediate or high risk for VTE (Khorana score ≥2)
    - Consider oral anticoagulant prophylaxis for up to 6 months[c,i]
      - Apixaban 2.5 mg PO BID
      - Rivaroxaban 10 mg PO QD
  - Low risk for VTE (Khorana score <2)
    - No routine VTE prophylaxis

[a] See VTE Risk Factors in Patients with Cancer (VTE-A).
[c] See Contraindications to VTE Prophylaxis (VTE-B).
[h] High-risk abdominal/pelvic cancer surgery patients include patients undergoing surgery for gastrointestinal malignancies, patients with a previous history of VTE, anesthesia time >2 hours, bed rest ≥4 days, advanced-stage disease, and patient age >60 years.
[i] For agent-specific contraindications, see Anticoagulant Options: Contraindications and Warnings (VTE-E, 3 of 4).

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VTE RISK ASSESSMENT MODELS AND PROPHYLAXIS IN PATIENTS WITH MULTIPLE MYELOMA RECEIVING IMiDs[i,j,k,l]

SAVED Score[m] for Patients Treated with IMiDs

Variable	Point Score
Surgery within 90 days	+2
Asian Race	-3
VTE history	+3
Age ≥80 years	+1
Dexamethasone (regimen dose) Standard dose (120–160 mg/cycle) High dose (>160 mg/cycle)	 +1 +2

→ Calculate risk

- High risk (≥2 points) → Recommended action:[n]
  - Enoxaparin 40 mg subcutaneous (SC) once daily
  - Dalteparin 5,000 units SC daily (category 2B)
  - Warfarin (international normalized ratio [INR] 2–3)
- Low risk (<2 points) → Recommended action:
  - No intervention
  - Aspirin 81–325 mg daily

[i] For agent-specific contraindications, see Anticoagulant Options: Contraindications and Warnings (VTE-E, 3 of 4).
[j] Agent selection based on: Renal failure (CrCl <30 mL/min), FDA approval, cost, ease of administration, monitoring, and ability to reverse anticoagulation.
[k] Follow institutional standard operating procedures (SOPs) for dosing schedules. If no SOPs then use the American College of Chest Physicians (ACCP) recommendations. (Kahn SR, et al. Chest 2012;141:e195S-226S; and Garcia DA, et al. Chest 2012;141:e24S-43S [journal.chestnet.org]).
[l] Following initiation of heparin: Hemoglobin, hematocrit, and platelet count every 2–3 days up to at least day 14 and every 2 weeks thereafter or as clinically indicated.
[m] Adapted from: Li A, Wu Q, Luo S, et al. Derivation and validation of a risk assessment model for immunomodulatory drug-associated thrombosis among patients with multiple myeloma. J Natl Compr Canc Netw 2019;17:840-847.
[n] Consider apixaban 2.5 mg PO BID as a possible choice for VTE prophylaxis in high-risk multiple myeloma patients. (Storrar NPF, et al. Br J Haematol 2019;185:142-144).

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VTE RISK ASSESSMENT MODELS AND PROPHYLAXIS IN PATIENTS WITH MULTIPLE MYELOMA RECEIVING IMiDs[i,j,k,l] (CONTINUED)

IMPEDE VTE Score[o]

Variable	Point Score
IMiD therapy	+4
BMI ≥25 kg/m^2	+1
Pelvic, hip, or femur fracture	+4
Erythropoiesis-stimulating agent	+1
Dexamethasone (regimen dose) Low dose (≤160 mg/month) High dose (>160 mg/month)	 +2 +4
Doxorubicin	+3
Ethnicity/Race = Asian/Pacific Islander	-3
History of VTE before multiple myeloma diagnosis	+5
Tunneled line or central venous catheter	+2
Existing thromboprophylaxis: therapeutic LMWH or warfarin	-4
Existing thromboprophylaxis: prophylactic LMWH or aspirin	-3

→ Calculate risk

High risk (>3 points) →
- Anticoagulant recommended[n] if not prescribed:
- Enoxaparin 40 mg SC once daily
- Dalteparin 5,000 units SC daily (category 2B)
- Warfarin (INR 2–3)

Low risk (≤3 points) →
- Recommended action:
- No intervention
- Aspirin 81–325 mg daily

[i] For agent-specific contraindications, see Anticoagulant Options: Contraindications and Warnings (VTE-E, 3 of 4).
[j] Agent selection based on: Renal failure (CrCl <30 mL/min), FDA approval, cost, ease of administration, monitoring, and ability to reverse anticoagulation.
[k] Follow institutional SOPs for dosing schedules. If no SOPs then use the ACCP recommendations. (Kahn SR, et al. Chest 2012;141:e195S-226S; and Garcia DA, et al. Chest 2012;141:e24S-43S [journal.chestnet.org]).
[l] Following initiation of heparin: Hemoglobin, hematocrit, and platelet count every 2–3 days up to at least day 14 and every 2 weeks thereafter or as clinically indicated.
[n] Consider apixaban 2.5 mg PO BID as a possible choice for VTE prophylaxis in high-risk multiple myeloma patients. (Storrar NPF, et al. Br J Haematol 2019;185:142-144.)
[o] Adapted from: Sanfilippo KM, Luo S, Wang TF, et al. Predicting venous thromboembolism in multiple myeloma: development and validation of the IMPEDE VTE score. Am J Hematol 2019;94:1176-1184.

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VTE RISK FACTORS IN PATIENTS WITH CANCER

General patient risk factors
- Active cancer
- Advanced stage of cancer
- Cancer types at higher risk:
  - Brain
  - Pancreas
  - Stomach
  - Bladder
  - Gynecologic
  - Lung
  - Lymphoma
  - Myeloproliferative neoplasms (MPN)
  - Kidney
  - Metastatic cancers
- Regional bulky lymphadenopathy with extrinsic vascular compression
- Familial and/or acquired hypercoagulability (including pregnancy)
- Medical comorbidities: Infection, renal disease, pulmonary disease, congestive heart failure (CHF), arterial thromboembolism
- Poor performance status
- Older age

Modifiable risk factors
- Smoking, tobacco
- Obesity
- Activity level/exercise

High-risk outpatients on chemotherapy, based on combinations of the following risk factors[1]
- Active cancers associated with high incidence of VTE: stomach, pancreas, lung, lymphoma, gynecologic, bladder, and testicular
- Prechemotherapy platelet count >350,000/mcL
- Prechemotherapy white blood cell (WBC) count >11,000/mcL
- Hemoglobin <10 g/dL
- Use of erythropoiesis-stimulating agents (ESAs)
- Body mass index (BMI) 35 kg/m^2 or greater
- Prior VTE

Treatment-related risk factors
- Major surgery
- Central venous catheter/IV catheter
- Chemotherapy such as:
  - IMiDs plus high-dose dexamethasone
  - Proteasome inhibitors
- Exogenous hormonal therapies such as:
  - Hormone replacement therapy (HRT)
  - Contraceptives[2]
  - Tamoxifen/raloxifene
  - Diethylstilbestrol

[1] Additional prospective randomized data are required to assess the benefit and safety of routine VTE prophylaxis in a cancer outpatient population with a favorable risk-benefit ratio. Listed risk factors are limited to cancer populations included in recent prospective, observational studies of solid tumor or lymphoma outpatients receiving chemotherapy [Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-4907; and Mandalà M, Barni S, Prins M, et al. Acquired and inherited risk factors for developing venous thromboembolism in patients with cancer receiving adjuvant chemotherapy: a prospective trial. Ann Oncol 2010;21:871-876.]

[2] The following hormonal contraceptives are associated with an increased risk of VTE: progestin-only injectables and combined hormonal contraceptives (containing estrogen + progestin) administered orally, by transdermal patch or vaginal ring. Progestin-only contraceptives administered orally or via implants or IUDs have not been definitively shown to increase the risk of VTE in the general population, but may contribute to VTE risk in patients with multiple risk factors. (Tepper NK, Whiteman MK, Marchbanks PA, et al. Progestin-only contraception and thromboembolism: a systematic review. Contraception 2016;94:678-700).

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CONTRAINDICATIONS TO VTE PROPHYLAXIS[1]

Contraindications to Prophylactic Anticoagulation

- **Active bleeding**
- **Thrombocytopenia (platelets <30,000–50,000/mcL or clinical judgment)[2]**
- **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[3,4]**
- **Interventional spine and pain procedures[5]**

Contraindications to Mechanical Prophylaxis

- **Absolute**
  - **Acute DVT**
  - **Severe arterial insufficiency (pertains to graduated compression stockings [GCS] only)**
- **Relative**
  - **Large hematoma**
  - **Skin ulcerations or wounds[6]**
  - **Thrombocytopenia (platelets <20,000/mcL)**
  - **Mild arterial insufficiency (pertains to GCS only)**
  - **Peripheral neuropathy (pertains to GCS only)**

[1] For agent-specific contraindications, see Anticoagulant Options: Contraindications and Warnings (VTE-E, 3 of 4).
[2] See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-G).
[3] 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.)
[4] 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 Communication. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on low molecular weight heparins. 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.
[5] 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.
[6] Skin ulcerations and wounds are more common with the use of GCS.

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PROPHYLACTIC ANTICOAGULATION OPTIONS FOR INPATIENTS AND SURGICAL ONCOLOGY OUTPATIENTS[1,2,3,4]

Options for Inpatients (VTE-1) or Surgical Oncology Outpatients (VTE-2)

Agent	Standard Dosing	Obesity Dosing (BMI ≥40 kg/m^2)[5]
LMWH: Dalteparin	5,000 units SC daily (category 1 for inpatient)	Consider 7,500 units SC daily (limited data)
LMWH: Enoxaparin	40 mg SC daily (category 1 for inpatient)	Consider 40 mg SC every 12 hours
Fondaparinux	2.5 mg SC daily (category 1 for inpatient)	Consider 5 mg SC daily (limited data)
UFH	5,000 units SC every 8–12 hours (category 1 for inpatient)	Consider 7,500 units SC every 8 hours

[1] Agent selection based on: Renal failure (CrCl <30 mL/min), FDA approval, cost, ease of administration, monitoring, and ability to reverse anticoagulation.
[2] Follow institutional SOPs for dosing schedules. If no SOPs then use the ACCP recommendations. (Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e195S-226S; and Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e24S-43S [journal.chestnet.org]).
[3] Following initiation of heparin: Hemoglobin, hematocrit, and platelet count every 2–3 days up to at least day 14 and every 2 weeks thereafter or as clinically indicated.
[4] For agent-specific contraindications, see Anticoagulant Options: Contraindications and Warnings (VTE-E, 3 of 4).
[5] Given the impact of renal insufficiency on clearance of enoxaparin and fondaparinux, UFH or dalteparin are recommended for obese patients with severe renal impairment (CrCl <30 mL/min).

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VTE RISK ASSESSMENT IN CANCER OUTPATIENTS

Khorana Predictive Model for Chemotherapy-Associated VTE[1]

Patient Characteristic	Risk Score
• Site of primary cancer	
▸ Very high risk (stomach, pancreas)	2
▸ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• Prechemotherapy platelet count 350 x 10^9/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 10^9/L	1
• BMI 35 kg/m^2 or higher	1

Total Score	Risk Category	Risk of Symptomatic VTE[2]
0	Low	0.3–1.5%
1, 2	Intermediate	1.8–4.8%
3 or higher	High	6.7–12.9%

[1] 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.
[2] Khorana AA. Cancer and Coagulation. Am J Hematol 2012;87 Supp 1:S82-87.

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NCCN Guidelines Version 1.2020
Acute Superficial Vein Thrombosis (SVT)

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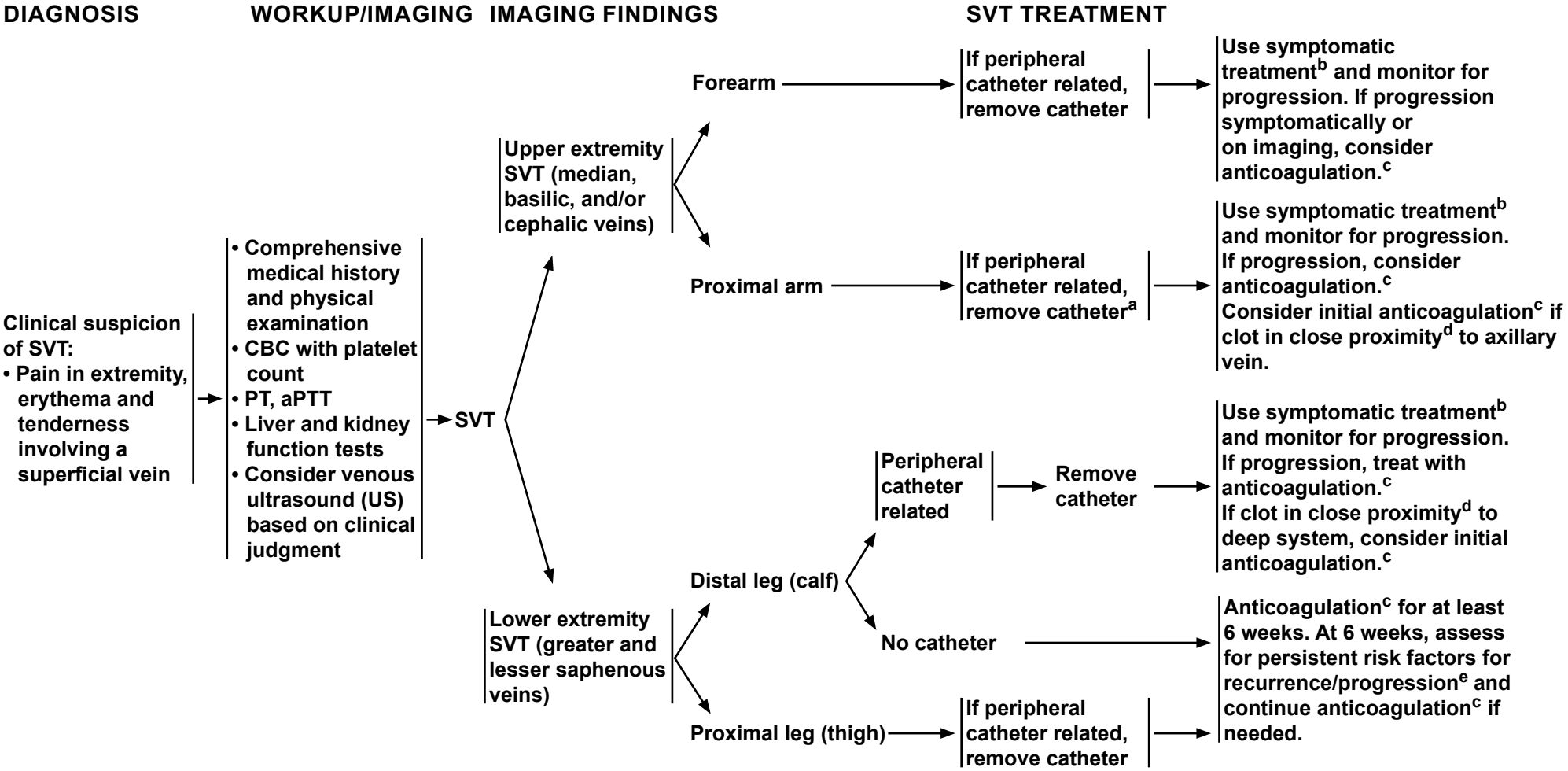

[a] For patients with SVT associated with a PICC line, catheter removal may not be necessary, especially if the patient is treated with anticoagulation and/or symptoms resolve.
[b] Symptomatic treatment includes warm compresses, nonsteroidal anti-inflammatory drugs (NSAIDs), and elevation.
[c] Rivaroxaban 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 cancer patients (Beyer-Westendorf J, al. Lancet Haematol 2017;4:e105-e113). Therapeutic dosing may be used at the clinician's discretion. See Therapeutic Anticoagulation for Venous Thromboembolism (VTE-E).
[d] Close proximity is defined as within approximately 3 cm.
[e] Longer duration of anticoagulation is recommended for patients with risk factors for clot recurrence/progression. Risk factors for clot recurrence/progression include: clot-related symptoms, especially if they do not resolve upon treatment; presence of multiple clots and/or clots that are not catheter-related; clot(s) that progress or are not resolved during initial treatment (with anticoagulation, catheter removal); advanced cancer stage; and undergoing active treatment for cancer, especially if treatment is associated with increased risk of VTE.

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NCCN Guidelines Version 1.2020
Acute Deep Vein Thrombosis (DVT)

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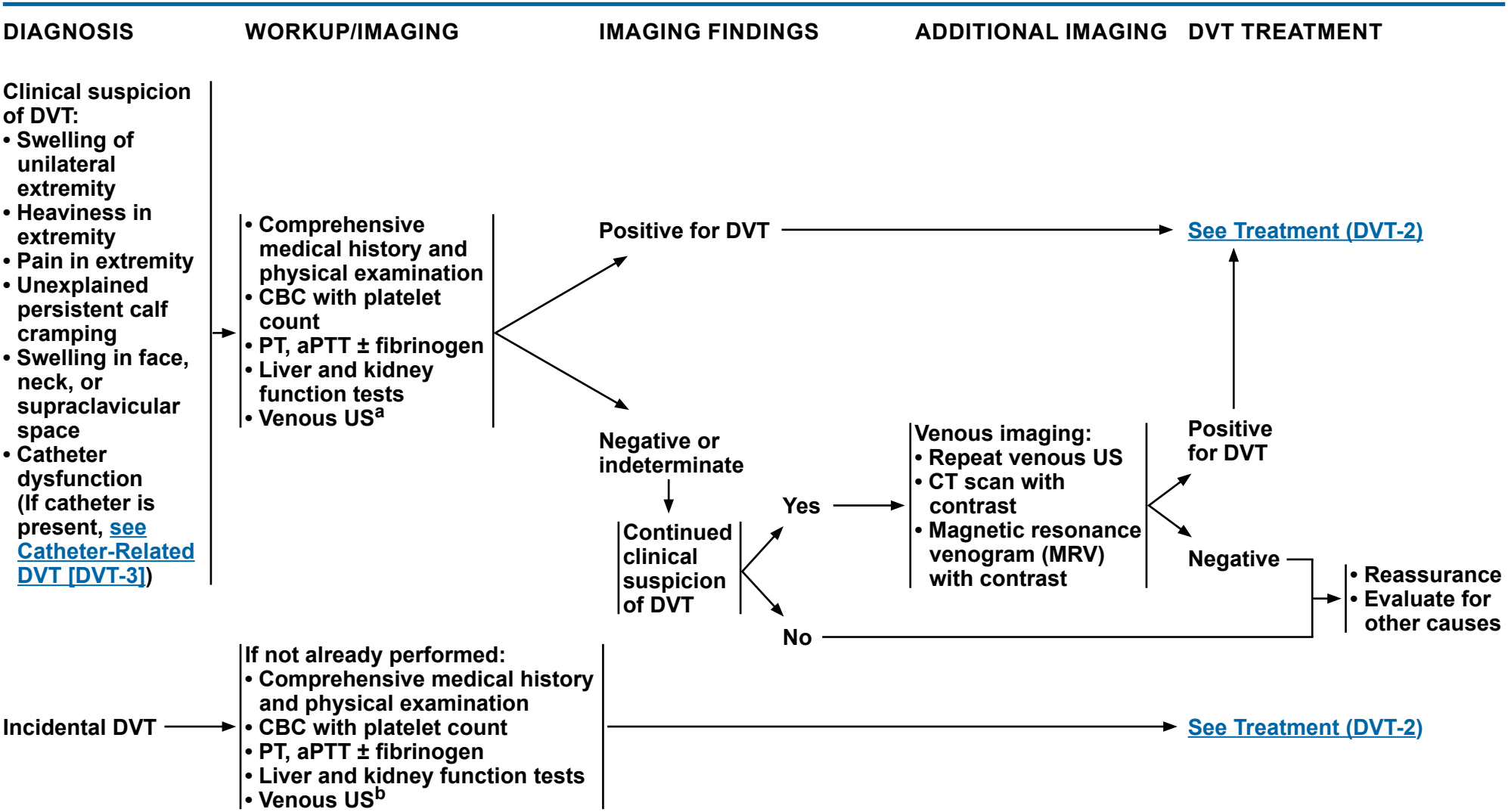

[a] In cases with high suspicion of DVT and no contraindications, consider initiating early anticoagulation while awaiting imaging results.
[b] If initial imaging results are inconclusive, consider venous US to confirm diagnosis.

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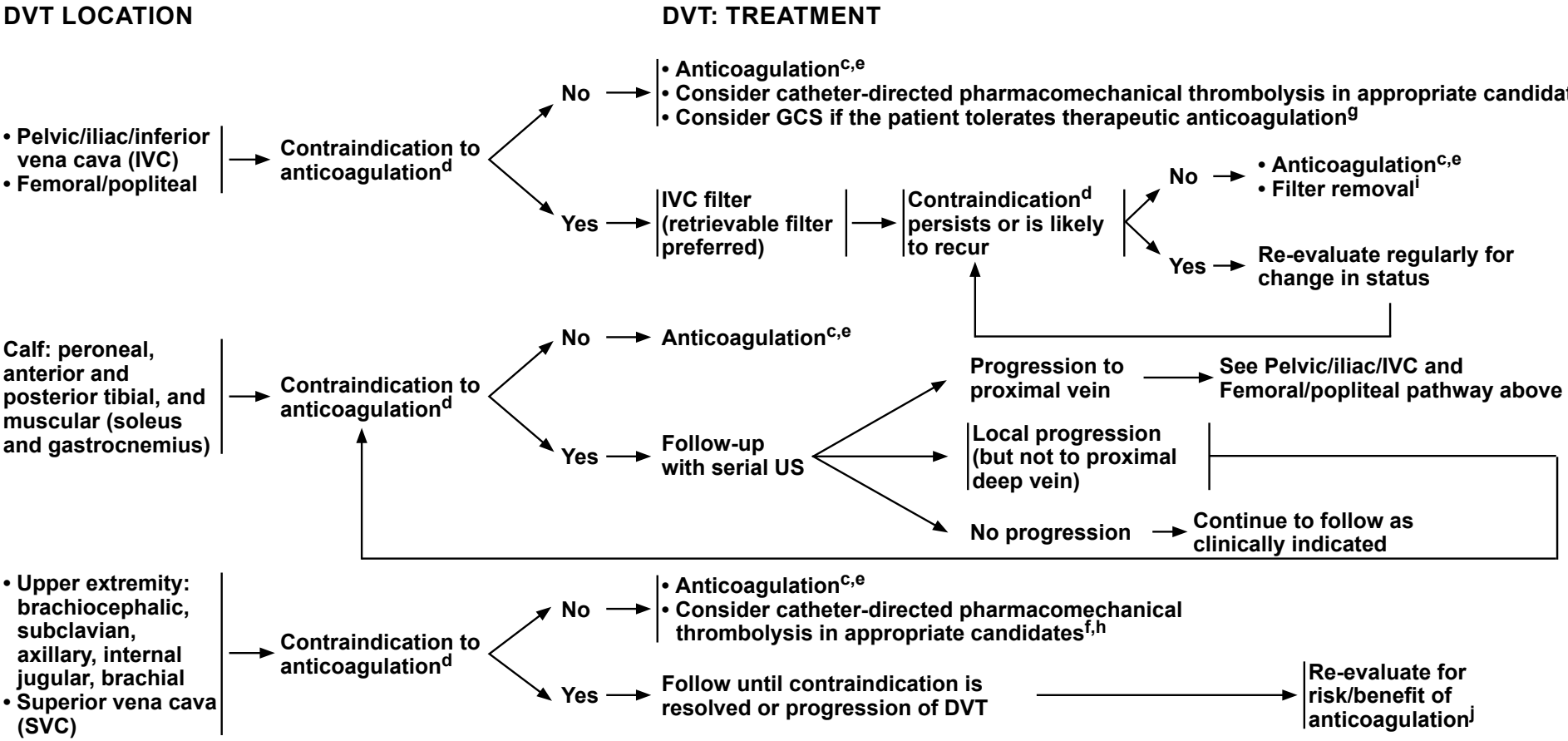

[c] See Therapeutic Anticoagulation for Venous Thromboembolism (VTE-E).
[d] See Contraindications to Therapeutic Anticoagulation (VTE-F). See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-G).
[e] See Therapeutic Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.
[f] Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. See Thrombolytic Agents (VTE-I). Appropriate candidates may include: patients who fail to respond to anticoagulation, those at risk of limb loss, and those with severe refractory proximal thrombosis. Candidates must have low bleeding risk.
[g] 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).
[h] See Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-J).
[i] Recommend IVC filter removal, if tolerating anticoagulation.
[j] See Elements for Consideration in Decision Not to Treat (VTE-K).

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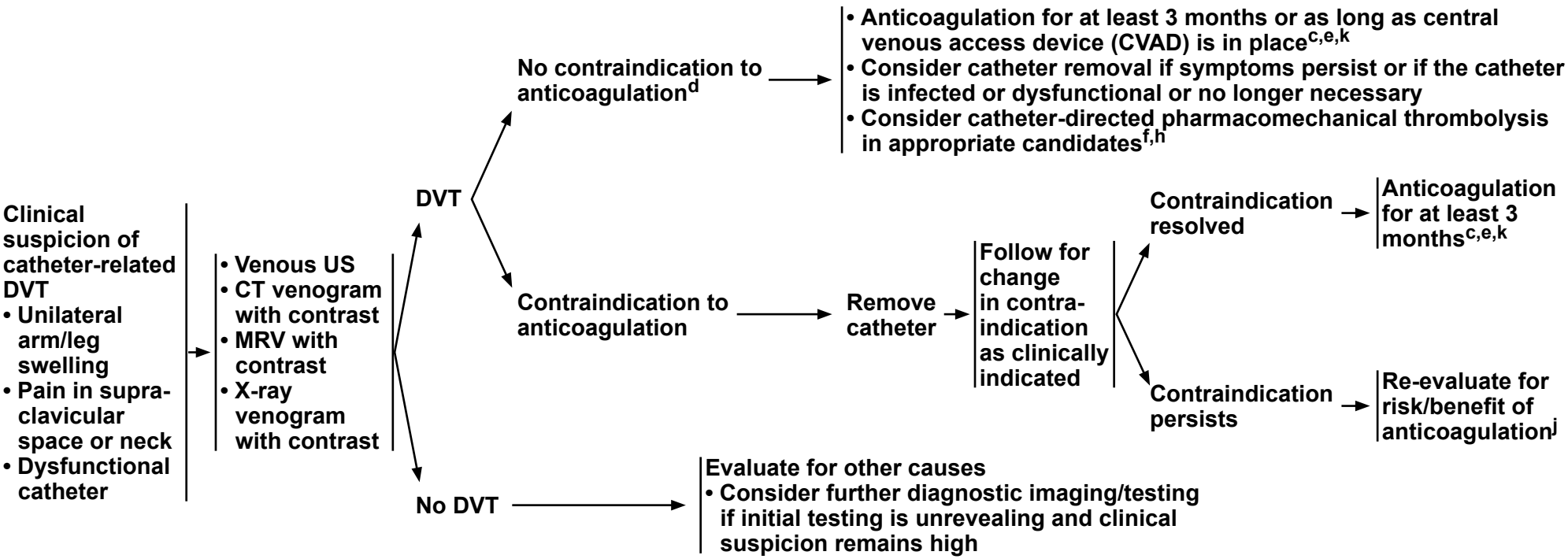
CATHETER-RELATED DVT: DIAGNOSIS AND TREATMENT



[c] See Therapeutic Anticoagulation for Venous Thromboembolism (VTE-E).
[d] See Contraindications to Therapeutic Anticoagulation (VTE-F). See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-G).
[e] See Therapeutic Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.
[f] Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. See Thrombolytic Agents (VTE-I). Appropriate candidates may include: patients who fail to respond to anticoagulation, those at risk of limb loss, and those with severe refractory proximal thrombosis. Candidates must have low bleeding risk.
[h] See Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-J).
[j] See Elements for Consideration in Decision Not to Treat (VTE-K).
[k] 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 patient tolerance of anticoagulation, response to anticoagulation, and catheter status. Consider longer duration anticoagulation in patients 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.

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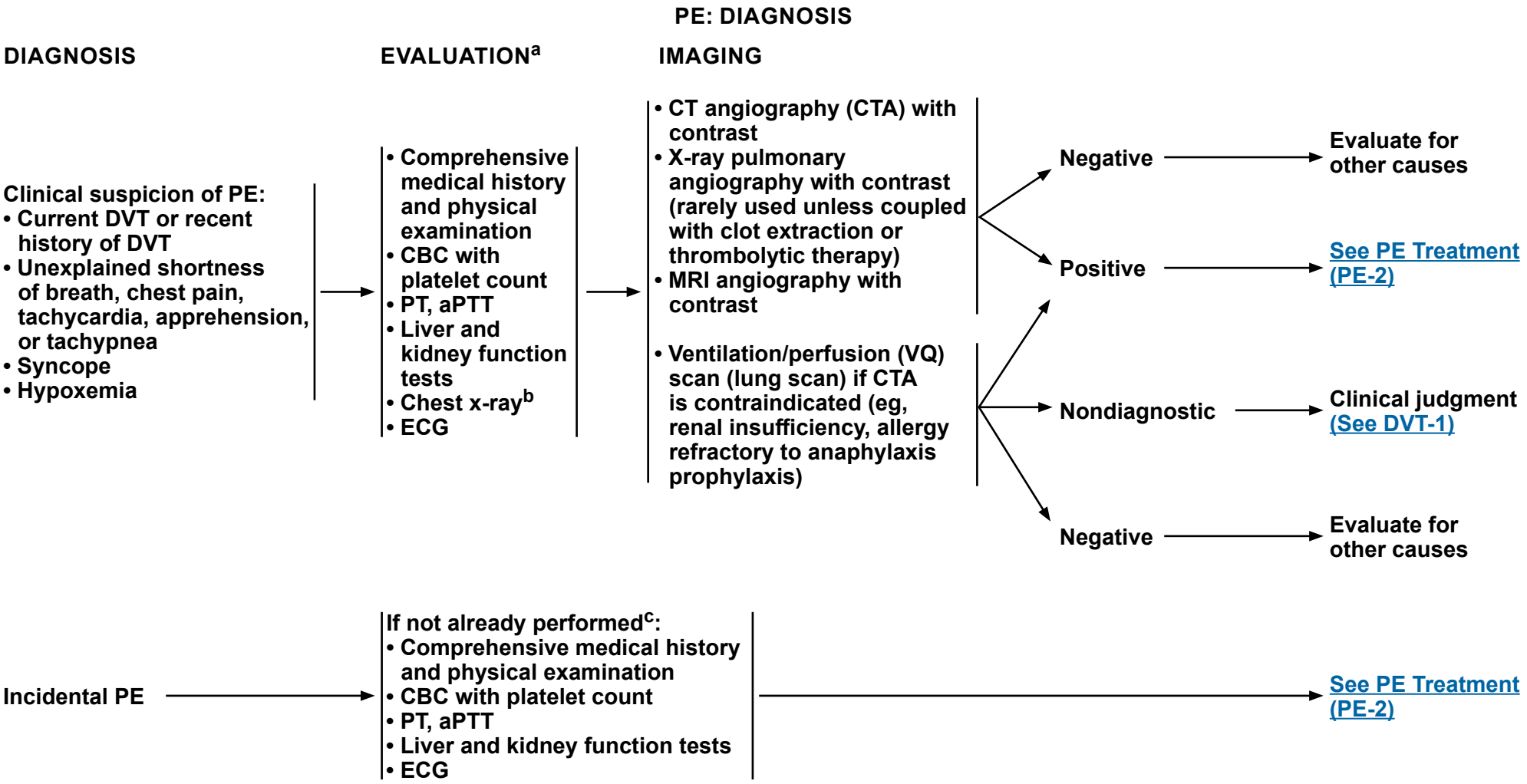
PE: DIAGNOSIS



[a] D-dimer has limited utility in patients with cancer.
[b] In cases with high suspicion of PE and no contraindications, consider initiating early anticoagulation while waiting for imaging results.
[c] Repeat imaging and diagnostic studies are not routinely needed in patients with incidental PE. Consider outpatient management for these patients.

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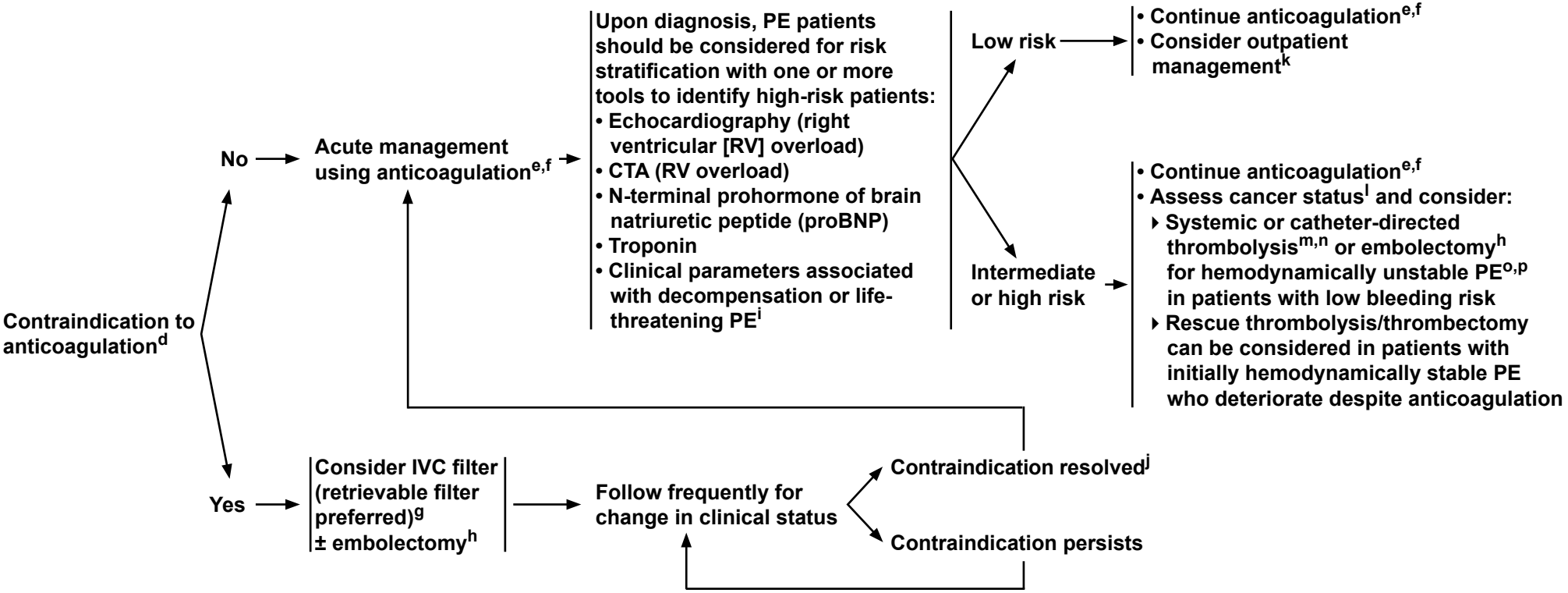
PE: TREATMENT



[d] See Contraindications to Therapeutic Anticoagulation (VTE-F). See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-G).
[e] See Therapeutic Anticoagulation for Venous Thromboembolism (VTE-E).
[f] See Therapeutic Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.
[g] 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).
[h] Consider embolectomy for treatment of massive PE (category 2B).
[i] 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.
[j] Recommend IVC filter removal, if tolerating anticoagulation therapy.
[k] Low-risk patients as identified by multimodality risk assessment (ie, clinical, laboratory, imaging) can be considered for outpatient management.
[l] See Elements for Consideration in Decision Not to Treat (VTE-K).
[m] See Thrombolytic Agents (VTE-I).
[n] See Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-J).
[o] 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.
[p] 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). See http://emcrit.org/emcrit/aha-pulmonary-embolism-guidelines-2011/.

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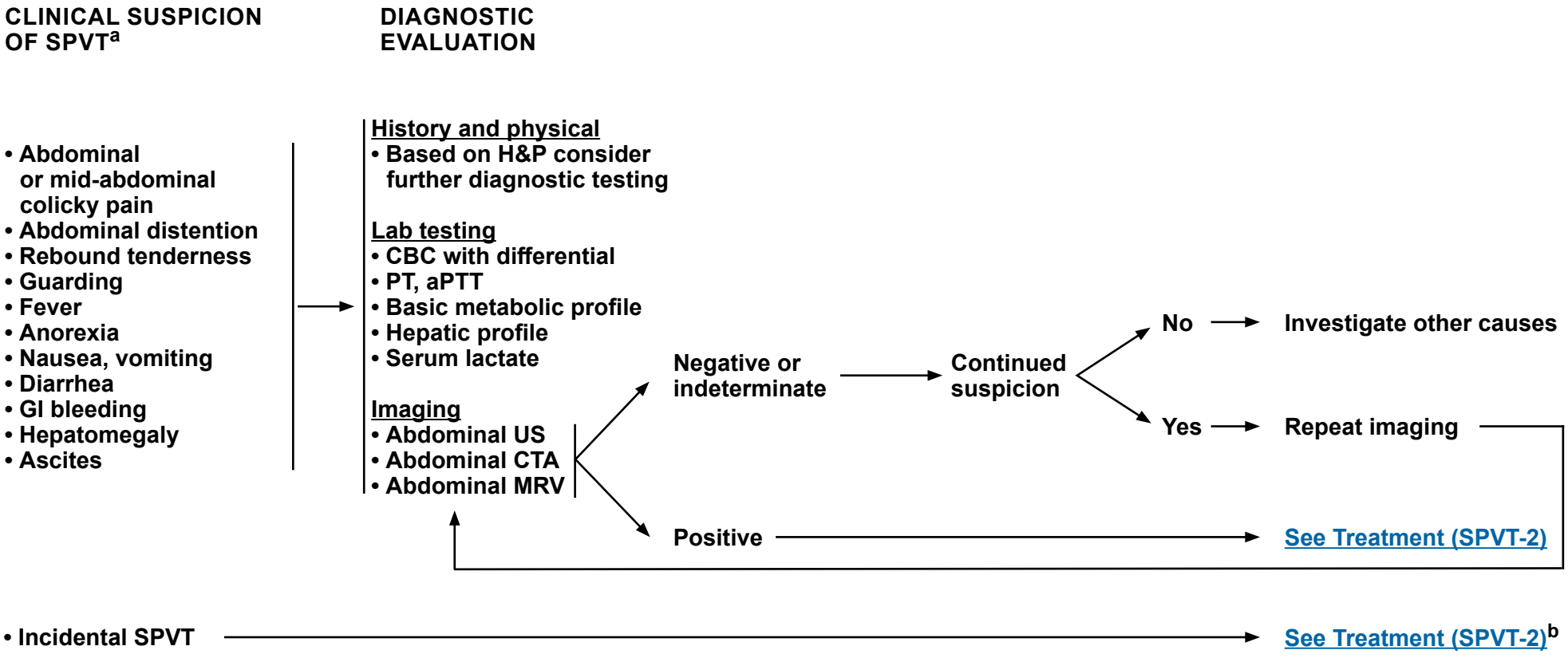
SPVT: DIAGNOSIS



[a] Risk factors relevant to cancer population for SPVT:
- Recent abdominal surgery (eg, splenectomy)
- Abdominal mass
- Pancreatitis
- Cirrhosis
- Exogenous estrogens
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Myeloproliferative neoplasms associated with the *JAK2* V617F mutation (most common) or *CALR* mutation (rare)

[b] For incidental SPVT, weigh the risks and benefits of anticoagulation therapy on an individual basis.

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SPVT: TREATMENT

SPVT LOCATION/ACUITY			TREATMENT
Acute Hepatic Vein Thrombosis • Symptoms/signs ≤8 weeks	Contraindication to anticoagulation[c]	No	• Anticoagulation[d,e] • Hepatology evaluation • Consider catheter-directed pharmacomechanical thrombectomy[f,g]
		Yes	• Hepatology evaluation • Reassess contraindications to anticoagulation regularly • Consider transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt
Chronic Hepatic Vein Thrombosis • Symptoms >8 weeks			• Hepatology evaluation • Consider TIPS or surgical shunt • Consider anticoagulation[d,e]
Acute Portal, Mesenteric, and/or Splenic Vein Thrombosis Symptoms/signs ≤8 weeks and No cavernous transformation/collaterals and No signs of portal hypertension	Contraindication to anticoagulation[c]	No	• Anticoagulation[d,e] • Surgery (if bowel infarction) • Consider catheter-directed pharmacomechanical thrombectomy[f,g]
		Yes	• Gastrointestinal/surgery evaluation • Surgery (if bowel infarction) • Reassess contraindications to anticoagulation regularly
Chronic, Portal, Mesenteric, and/or Splenic Vein Thrombosis Symptoms >8 weeks or Cavernous transformation/collaterals noted or Signs of portal hypertension			• Gastrointestinal evaluation • Beta blockade • Consider variceal banding or sclerosis • Consider anticoagulation[d,e]

[c] See Contraindications to Therapeutic Anticoagulation (VTE-F). See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-G).
[d] 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.
[e] See Therapeutic Anticoagulation for Venous Thromboembolism (VTE-E).
[f] 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-I).
[g] See Contraindications to Thrombolysis and Indications for Thrombolysis (VTE-J).

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THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM

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.[1]**
  - **Duration of Anticoagulation as Recommended by Guideline:**
    - **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 catheter-associated thrombosis, anticoagulate as long as 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-K)
- **Select regimen based on these factors (not in order of importance): Renal failure (creatinine clearance [CrCl] <30 mL/min), hepatic disease (elevated transaminases or bilirubin, Child-Pugh B and C liver impairment, or cirrhosis), inpatient/outpatient, FDA approval, cost, patient preference, ease of administration, monitoring, bleeding risk assessment, and ability to reverse anticoagulation. See Contraindications and Warnings on VTE-E, 3 of 4.**
- **Baseline laboratory testing: CBC, renal and hepatic function panel, aPTT, and PT/INR.**
- **Follow institutional SOPs for dosing schedules. If there are no SOPs, then use the ACCP recommendations.[2]**
- **Following initiation of anticoagulant: Hemoglobin, hematocrit, and platelet count at least every 2–3 days for the first 14 days and every 2 weeks thereafter or as clinically indicated.**

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References

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM (CONTINUED)

DOACs (preferred for patients without gastric or gastroesophageal lesions)[a]
- Apixaban (category 1)
  - 10 mg PO BID for 7 days followed by 5 mg PO BID[12-15]
- Edoxaban (category 1)
  - Initial therapy with LMWH[b,3,4] or UFH[c,5] 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 inhibitors)[d,6,7]
- Rivaroxaban
  - 15 mg PO BID for the first 21 days followed by 20 mg daily[8-11]

LMWH (preferred for patients with gastric or gastroesophageal lesions)
- Dalteparin (category 1)
  - 200 units/kg SC daily for 30 days, then switch to 150 units/kg once daily[e,4,16,17]
- Enoxaparin
  - 1 mg/kg SC every 12 hours (can consider decreasing intensity to 1.5 mg/kg daily after first month)[f,3,18-20]

DOACs (if above regimens not appropriate or unavailable)[a]
- Dabigatran
  - Initial therapy with LMWH[b,3,4] or UFH[c,5] for at least 5 days followed by dabigatran 150 mg PO BID[d,21,22]

Fondaparinux[23,24]
- 5 mg SC daily (<50 kg)
- 7.5 mg SC daily (50–100 kg)
- 10 mg SC daily (>100 kg)

UFH (category 2B)[5]
- 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 BID (category 2B)
- SC 333 units/kg load, followed by 250 units/kg every 12 hours[25]

Warfarin[g,26-28]
- 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)
  - LMWH[3,4] + warfarin[g] options:
    - Dalteparin 200 units/kg SC daily[4] or 100 units/kg SC every 12 hours
    - Enoxaparin 1 mg/kg SC every 12 hours[3]
  - Fondaparinux + warfarin[g,23,24]
    - 5 mg SC daily (<50 kg)
    - 7.5 mg SC daily (50–100 kg)
    - 10 mg SC daily (>100 kg)
  - UFH[5] + warfarin[g] 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

[a] Patients with gastric and gastroesophageal tumors are at increased risk for hemorrhage with direct oral anticoagulants (DOACs).[29]

[b] LMWH dosing options:
- Dalteparin 200 units/kg SC daily
- Enoxaparin 1 mg/kg SC every 12 hours

[c] UFH dosing options:
- IV 80 units/kg bolus, followed by 18 units/kg/h, adjusted to a 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

[d] 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.

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

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

[g] 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 ≥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 monthly.

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References

ANTICOAGULANT OPTIONS: CONTRAINDICATIONS AND WARNINGS

Agent(s)	Contraindications and Warnings
LMWH	• Use with caution in patients with renal dysfunction. Consider dose adjustments or alternative therapy for patients with severe renal disfunction (CrCl <30 mL/min). • Follow package insert for renal dysfunction and body weight dosing. • Anti-Xa monitoring (peak and trough) of LMWH has been recommended for patients with severe renal dysfunction, although limited data are available to support the clinical relevance of anti-Xa levels. • Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Fondaparinux	• Contraindicated in patients with CrCl <30 mL/min • Use with caution in patients with moderate renal insufficiency (CrCl 30–50 mL/min), weight <50 kg, or age >75 y
UFH	• Absolute contraindication: recent/acute HIT • Relative contraindication: past history of HIT
Warfarin	Relative contraindications: • Concomitant inhibitors and inducers of CYP2C9, 1A2, or 3A4
DOACs: Apixaban, dabigatran, edoxaban, and rivaroxaban	Contraindications: • Stage IV/V chronic kidney disease: ▸ Apixaban[h]: CrCl <25 mL/min ▸ Dabigatran, edoxaban, and rivaroxaban: CrCl <30 mL/min • Active/clinically significant liver disease: ▸ Apixaban or edoxaban: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN; total bilirubin >1.5 x ULN ▸ Dabigatran or rivaroxaban: ALT/AST >3x ULN • Strong dual inhibitors/inducers of CYP3A4 and P-glycoprotein (P-gp): see prescribing information for rivaroxaban[8] and apixaban[12] • Inducers/inhibitors of P-gp: see prescribing information for dabigatran[21] and edoxaban[6] Relative contraindications, use with caution: • DOACs have been associated with an increased risk of gastrointestinal and possibly genitourinary tract bleeding, and should be used with caution in patients with genitourinary or gastrointestinal tract lesions, pathology, or instrumentation. • Use with caution in patients with compromised renal or liver function. • For patients receiving nephrotoxic or hepatotoxic chemotherapy consider monitoring patients more closely with laboratory testing. • Consider drug-drug interactions.

[h] 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 data to support safe apixaban dosing in these patients, especially those who are on hemodialysis.

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References

THERAPEUTIC ANTICOAGULATION FOR VENOUS THROMBOEMBOLISM
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[4] Prescribing information: Dalteparin sodium injection, for subcutaneous use; 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020287s069lbl.pdf.
[5] Prescribing information: Heparin sodium injection for intravenous or subcutaneous use; 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017029s140lbl.pdf.
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CONTRAINDICATIONS TO THERAPEUTIC ANTICOAGULATION[1]

- **Absolute contraindications**
  - **Active bleeding (major)[2]**
  - **Indwelling neuraxial catheters**
  - **Neuraxial anesthesia/lumbar puncture[3,4]**
  - **Interventional spine and pain procedures[5]**

- **Relative contraindications**
  - **Chronic, clinically significant measurable bleeding >48 hours**
  - **Thrombocytopenia (platelets <30,000–50,000/mcL or clinical judgment)[6]**
  - **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)**
  - **CNS metastases[7]**
  - **Long-term antiplatelet therapy[8]**

[1] For agent-specific contraindications, see VTE-E, 3 of 4.
[2] Active bleeding with >2 units transfused, decrease in hemoglobin by ≥2 g/dL, or intracranial or intraspinal bleeding.
[3] 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.)
[4] 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 Communication. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on low molecular weight heparins. 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.
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[6] See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-G).
[7] 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.
[8] For patients on long-term antiplatelet therapy, reassess need for antiplatelet therapy and discontinue/reduce dose of antiplatelet treatment if possible.

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

Background:

- **Development of thrombocytopenia is common in cancer patients. Thrombocytopenia increases the risk of bleeding in the setting of therapeutic anticoagulation for VTE.**
- **In cancer patients on therapeutic anticoagulation:**
  - **In >75% of patients with platelet counts <50,000/mcL, the thrombocytopenia was due to chemotherapy.**
  - **Confirmed HIT is estimated to represent <1% of thrombocytopenic episodes.**

Enoxaparin Dose Modification in the Setting of Thrombocytopenia

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

- **For patients at high risk for recurrent VTE and anticipated prolonged thrombocytopenia, transfusion of platelets to maintain platelet count of >25,000/mcL to allow for continuation of enoxaparin may be appropriate.**
- **These guidelines are based on limited data.**
- **When using apixaban, edoxaban, or rivaroxaban in the setting of thrombocytopenia, hold until platelet count recovers to >50,000/mcL.**

Reference: Mantha S, Miao Y, Wills J, et al. Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis 2017;43:514-518.

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THERAPEUTIC ANTICOAGULATION FAILURE[1]

Anticoagulation Agent	Check	Results	Action
UFH	• aPTT levels • UFH anti-factor Xa levels	Therapeutic aPTT[2]/ UFH anti-factor Xa level	• Consider HIT[3] • Consider lupus inhibitor/anticoagulant[4] • Increase dose of UFH or switch to one of the following: LMWH, fondaparinux, or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)
		Sub-therapeutic aPTT/ UFH anti-factor Xa level	• Consider HIT[3] • Consider alternative anticoagulant • Increase dose of UFH to reach therapeutic level • Check antithrombin (AT) level if UHF dose exceeds 25 units/kg/h[5,6]
LMWH			• Consider HIT[3] • Move to every-12-hour schedule, increase dose,[7,8] or switch to fondaparinux or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)
Fondaparinux			• Consider HIT[3] • Switch to UFH, LMWH, or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)
Warfarin[3]	• INR	Therapeutic INR	• Switch to LMWH, UFH, fondaparinux, or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)
		Sub-therapeutic INR	• Increase warfarin dose and treat with parenteral agent until INR target achieved or consider switching to LMWH, UFH, fondaparinux, or DOAC (apixaban, edoxaban, or rivaroxaban; all category 2B)
Apixaban, dabigatran, edoxaban, rivaroxaban			• Switch to LMWH[9] • Switch to fondaparinux

[1] Anticoagulation failure is defined as an extension of DVT or new DVT or PE while on therapeutic levels of recommended anticoagulation therapy. See Therapeutic Anticoagulation for Venous Thromboembolism (VTE-E).
[2] Therapeutic aPTT range is based on hospital SOP range or 2.0–2.5 x control, if local ranges are unavailable.
[3] Evaluate for HIT (HIT-1). If clinical suspicion of HIT is high, see (HIT-1).
[4] Lupus inhibitor may prolong aPTT giving the false impression of therapeutic aPTT. Check UFH (anti-Xa) level and lupus inhibitor testing to investigate. If lupus inhibitor present, use UFH (anti-Xa) levels to monitor UFH.
[5] Heparin resistance may be suspected when UFH dose exceeds 25 units/kg/h in the setting of a subtherapeutic aPTT.
[6] If AT level <50%, consider AT supplementation versus alternative anticoagulant (eg, direct thrombin inhibitor [DTI], DOAC); if AT level >50%, consider alternative anticoagulant (ie, LMWH, fondaparinux, DOAC).
[7] LMWH (anti-Xa) levels may be considered in patients who are underweight, obese, renally impaired, or for whom compliance is a concern. LMWH (anti-Xa) levels should be checked at their peak at 4 hours after dosing for both twice-daily and once-daily dosing regimens. Reference ranges are not clinically validated and can vary by facility.
[8] 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).
[9] If DOAC failure is thought to be due to medication non-adherence, warfarin is a second-line option as it allows for more convenient laboratory drug monitoring.

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THROMBOLYTIC AGENTS

- **Deep Vein Thrombosis:**[1,2]
  - **Pharmacomechanical devices**[2,3]
    - ◊ **Alteplase 10 mg to 25 mg per session**
  - **Infusion catheters**[2,3]
    - ◊ **Alteplase 0.5 mg to 1 mg per hour for 12–24 hours**
    - ◊ **Reteplase 0.5 units to 1 units per hour for 12–24 hours**
- **Pulmonary Embolism**
  - **Systemic thrombolysis**
    - ◊ **Alteplase 100 mg IV over 2 hours**[5]
    - ◊ **Alteplase 50 mg as a 10 mg bolus followed by 20 mg per hour for 2 hours**[4,5]
    - ◊ **Tenecteplase (category 2B)**[6]

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

  - **US-assisted, catheter-directed thrombolysis**[7]
    - ◊ **Alteplase 1 mg per hour per lung for 12–24 hours**[8]

[1] A post-procedural imaging study is recommended to confirm the results of thrombolysis.
[2] Different FDA-approved catheters and devices exist to deliver thrombolytic agent 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.
[3] Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017;377:2240-2252.
[4] 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.
[5] Altepase 50 mg may be appropriate for patients aged >75 years, with recent surgery (within 1 mo), or with high risk of bleed.
[6] Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-1411.
[7] 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.
[8] US-assisted, catheter-directed thrombolysis has been used for PE patients 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.

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CONTRAINDICATIONS TO THROMBOLYSIS AND INDICATIONS FOR THROMBOLYSIS

Contraindications to Thrombolysis[1,2]

- **Absolute**
  - History of hemorrhagic stroke or stroke of unknown origin
  - 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 mm^3
  - 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
- Symptomatic iliofemoral thrombosis
- Massive/life-threatening PE
- Intestinal SPVT with high risk of ischemia

[1] 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)(Supple):e419S-e494S.
[2] The risks and benefits of thrombolysis should be assessed on a case-by-case basis by the clinician caring for the patient.

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ELEMENTS FOR CONSIDERATION IN DECISION NOT TO TREAT

- **Patient refusal**
- **No therapeutic advantage**
  - **Limited survival**
  - **High 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**

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REVERSAL OF ANTICOAGULATION IN THE EVENT OF LIFE-THREATENING BLEEDING OR EMERGENT SURGERY

- In the event of 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 incumbent on the provider to keep in stock the recommended reversal agents for all anticoagulants included in these tables:
  - 4-factor prothrombin complex concentrate (4-factor PCC)
  - andexanet alfa
  - desmopressin (DDAVP)
  - fresh frozen plasma (FFP)
  - idarucizumab
  - oral charcoal
  - protamine
  - rhFVIIa activated prothrombin complex concentrates (aPCC) (anti-inhibitor coagulant complex, vapor heated)
  - vitamin K_1 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)	• 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) • Follow aPTT closely • Maximum dose: 50 mg Examples: ▸ Patient bleeds immediately after 5000 unit bolus is given 50 mg of protamine ▸ 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	• Protamine can cause anaphylaxis if administered too rapidly. • Patients with fish allergies, previous exposure to protamine (eg, NPH insulin), or vasectomized or infertile men are at increased risk. • Excessive protamine (protamine: heparin ratios >1.3:1 mg/U) are associated with platelet dysfunction and decreased thrombin activity, resulting in bleeding. • Protamine reverses a variable amount of LMWH anti-Xa activity.
• LMWH (Half-life 5–7 hours)	• Protamine 1 mg/mg of enoxaparin or 1 mg/100 units of dalteparin within 8 hours of dose • Protamine 0.5 mg/mg of enoxaparin or 0.5 mg/100 units of dalteparin if dose administered >8 hours prior • If >12 hours since dose, consider clinical scenario (eg, LMWH dose, renal function, bleeding severity) when deciding whether protamine is indicated • Administer protamine by slow IV infusion (no faster than 5 mg per min) • Maximum dose: 50 mg	

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References

REVERSAL OF ANTICOAGULATION: MANAGEMENT OF SUPRATHERAPEUTIC INR

Warfarin (effective half-life 20–60 hours)	Reversal of Anticoagulation	Precautions/Additional Considerations
• INR 4.5–10, no bleeding	• Hold warfarin dose. • Look for drug or dietary interactions and eliminate them if possible. • Look for evidence of acute hepatic dysfunction/injury. • Follow INR closely[1] (at least daily as an inpatient, every 1–2 days as outpatient). • When INR approaches therapeutic range (INR <4) restart warfarin at reduced dose (10%–20% dose reduction) if causal factor not present or cannot be eliminated. • Recheck INR within 4–7 days. • Adjust warfarin dose based on weekly INR until stable.	• N/A
• INR >10, no bleeding	• Hold warfarin dose. • Consider small dose of oral vitamin K_1 1–2.5 mg in patients at high risk of bleeding (may repeat dose in 24 h if INR remains elevated). • Look for drug or dietary interactions and eliminate them if possible. • Look for evidence of acute hepatic dysfunction/injury. • Follow INR closely[1] (at least daily as an inpatient, every 1–2 days as outpatient). • When INR approaches therapeutic range (INR <4) restart warfarin at reduced dose (at least 20% dose reduction) if causal factor not present or cannot be eliminated. • Recheck INR within 4–7 days. • Adjust warfarin dose based on weekly INR until stable.	• Avoid vitamin K_1 SC administration due to erratic absorption, and delayed onset compared with oral administration. • Vitamin K_1 IV administration can be used for more rapid absorption than tablets.

[1] The impact of warfarin dose changes can take at least 5–7 days to be fully manifested in the INR.

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REVERSAL OF ANTICOAGULATION IN THE EVENT OF LIFE-THREATENING BLEEDING OR EMERGENT SURGERY

Warfarin (effective half-life 20–60 hours)	Reversal of Anticoagulation	Precautions/Additional Considerations
• Management of urgent surgery (within 24–48 hours)	Within 24 hours: • Hold warfarin dose • Administer vitamin K_1 1–2.5 mg IV slowly (no faster than 1 mg/min) • Repeat INR pre-operation to determine need for supplemental FFP Within 48 hours: • Hold warfarin dose • Administer vitamin K_1 2.5 mg orally • Repeat INR at 24 and 48 hours to assess need for supplemental vitamin K_1 or FFP	• Infection due to pathogen transmission (all plasma-derived agents; greater risk with FFP compared with solvent/detergent-treated products [3- or 4-factor PCC, aPCC]) • Immune reactions, including allergic/anaphylactic, alloimmunization (vitamin K_1 and all plasma-derived agents; greater risk with FFP compared with solvent/detergent-treated products [3- or 4-factor PCC, aPCC]) • Excessive intravascular volume (FFP) • Transfusion-related acute lung injury (FFP) • Pulmonary edema (FFP) • Agglutination reactions/hemolysis due to blood-type incompatibility (FFP) • Transfusion-associated graft-versus-host disease (if not irradiated FFP) • Febrile nonhemolytic transfusion reactions (FFP)
• Life-threatening bleeding	• Hold warfarin dose • Administer vitamin K_1 10 mg IV slowly (no faster than 1 mg/min) • Administer 4-factor PCC ▸ 4-factor PCC dosing (based on units of Factor IX per kg of actual body weight) ◊ INR 2–<4: 25 units/kg (maximum 2,500 units) ◊ INR 4–6: 35 units/kg (maximum 3,500 units) ◊ INR >6: 50 units/kg (maximum 5,000 units) ▸ If 4-factor PCC unavailable or patient is allergic to heparin and/or a history of HIT in the last 12 months: ◊ INR <4: 3-factor PCC 25 units/kg + FFP 2–3 units ◊ INR >4: 3-factor PCC 50 units/kg + FFP 2–3 units ▸ FFP 15 mL/kg (consider if PCC not available) ▸ rhFVIIa 25 mcg/kg (consider if PCC unavailable or bleeding is unresponsive to PCC) • Monitor INR closely	• Three hours or longer may be required for phytonadione to halt or slow active bleeding. Rapid administration of IV vitamin K_1 is associated with a higher risk of anaphylaxis (risk ~1 in 3,000 doses). • Monitor vital signs closely. • Administer 4-factor PCC IV push at a rate not exceeding 5 mL/min. 4-factor PCC is associated with thromboembolism within 30 days of administration. • Administer 3-factor PCC IV push at a rate not exceeding 10 mL/min. • FFP is associated with thromboembolism within 30 days of administration. • Administer rhFVIIa IV push over 2–5 minutes. • rhFVIIa has been associated with thromboembolic events. • For patients with a history of HIT use 3-factor PCC without heparin[2] (Factor IX complex).

[2] Prescribing information: Factor IX complex Profilnine. 2014.

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References

REVERSAL OF ANTICOAGULATION IN THE EVENT OF LIFE-THREATENING BLEEDING OR EMERGENT SURGERY

Direct Thrombin Inhibitor (DTI)	Reversal of Anticoagulation	Precautions/Additional Considerations
• Bivalirudin[3] (half-life 25 minutes with normal renal function)	• Discontinue drug. • No specific antidote exists, but beneficial effects have been ascribed to the following: ‣ Hemofiltration and hemodialysis are effective in removal of bivalirudin. ‣ 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. ‣ DDAVP 0.3 mcg/kg reduced bleeding in animal and ex-vivo models, and if used should be administered over 15–30 minutes.	• Limited data exist to support all reversal strategies. • Repeated doses (more than 3 or 4) of DDAVP are associated with tachyphylaxis and hyponatremia.
• Argatroban[4] (half-life 45 minutes with normal hepatic function)	• Discontinue drug. • No specific antidote exists, but beneficial effects have been ascribed to the following: ‣ Animal models and case reports suggest PCCs and aPCCs (50–100 units/kg IV) may be effective. ‣ Ex-vivo studies suggest rhFVIIa (90 mcg/kg IV) also may be effective. ‣ DDAVP (0.3 mcg/kg) reduced bleeding in animal and ex-vivo models. ‣ Monitor reversal with aPTT.	

[3] 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.
[4] 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.

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REVERSAL OF ANTICOAGULATION IN THE EVENT OF LIFE-THREATENING BLEEDING OR EMERGENT SURGERY

Direct Thrombin Inhibitor (DTI)	Reversal of Anticoagulation	Precautions/Additional Considerations
• Dabigatran[4] (half-life 14–17 hours)	• Discontinue drug. • Adminster idarucizumab, 2.5 g in 2 consecutive boluses. • Oral charcoal if dose within 2 hours of ingestion ▸ standard initial adult dose 50–100 g followed by doses every 1, 2, or 4 hours equivalent to 12.5 g/h • For special situations with slow or incomplete clearance (eg, renal dysfunction or failure), consider adding to idarucizumab: ▸ Hemodialysis ▸ Hemodialysis with a charcoal filter • Monitor reversal with aPTT or dilute TT or Hemoclot thrombin inhibitor test to ensure complete reversal.	• Limited data exist to support all reversal strategies. • In patients with renal failure/severe renal insufficiency, dialysis may be helpful in addition to idarucizumab. • Idarucizumab is associated with thromboembolism within 30 days.

Factor Xa Inhibitor	Reversal of Anticoagulation	Precautions/Additional Considerations
• Fondaparinux (half-life 17–21 hours)	• Discontinue drug. No specific antidote exists; however, limited data suggest rhFVIIa (90 mcg/kg IV) may be beneficial.	• rhFVIIa has been associated with thromboembolic events.

[4] 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.

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REVERSAL OF ANTICOAGULATION IN THE EVENT OF LIFE-THREATENING BLEEDING OR EMERGENT SURGERY

Direct Factor Xa Inhibitor	Reversal of Anticoagulation	Precautions/Additional Considerations
• Rivaroxaban (Half-life 9–12 hours; upper level for elderly) OR • Apixaban (Half-life 12 hours)	Discontinue drug. Beneficial effects have been ascribed to the following: • Consider oral charcoal if dose within 2 hours of ingestion and repeat within 6 hours ‣ Standard initial adult dose 50–100 g followed by doses every 1, 2, or 4 hours equivalent to 12.5 g/h • Administer: ‣ Andexanet alfa (consider for patients with intracranial hemorrhage) ‣ Alternative options may include: ◊ aPCC 25–50 units/kg IV ◊ 4-factor PCC 25–50 units per kg (based on units of Factor IX per kg of actual body weight) or fixed dose of 2,000 units ◊ If 4-factor PCC is unavailable or patient is allergic to heparin and/or 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)	• See andexanet alfa dosing and administration tables VTE-L 7 of 8 • Andexanet alfa is associated with thromboembolism within 30 days of administration • rhFVIIa has been associated with thromboembolic events • aPCC and 4-factor PCC have been associated with thromboembolism when used for reversal of direct factor Xa inhibitors
• Edoxaban (Half-life 10–14 hours)	Discontinue drug. No specific antidote exists. Beneficial effects have been ascribed to the following: • Consider oral charcoal if dose within 2 hours of edoxaban dose and repeat within 6 hours: standard initial adult dose 50–100 g followed by doses every 1, 2, or 4 hours equivalent to 12.5 g/h • May be helpful based on in vitro and animal models. • Administer: ‣ aPCC 25–50 units/kg IV or ‣ 4-factor PCC 25–50 units per kg (based on units of Factor IX per kg of actual body weight) or ‣ rhFVIIa 20–120 mcg/kg IV ‣ If 4-factor PCC is unavailable or patient is allergic to heparin and/or 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)	• rhFVIIa has been associated with thromboembolic events • aPCC and 4-factor PCC have been associated with thromboembolism when used for reversal of direct factor Xa inhibitors

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References

ANDEXANET ALFA DOSING AND ADMINISTRATION

Table 1: Andexanet Alfa Dosing Strategy§

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

Table 2: Andexanet Alfa Low- and High-Dose Strategies and Administration Instructions§

Dose*	Initial IV Bolus (administered at a rate of 30 mg/min)	IV Infusion¥
Low-dose	400 mg	500 mg administered over 125 minutes (4 mg/min)
High-dose	800 mg	1,000 mg administered over 125 minutes (8 mg/min)

§ Prescribing Information: Coagulation factor Xa (recombinant), ic Lyophilized Powder for Solution For Intravenous Injection; 2018. Available at: https://www.fda.gov/media/113279/download.

* 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, the IV infusion dosing recommendations above differ from the package insert prescribing information in order to round doses to the closest available vial size.

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References

REVERSAL OF ANTICOAGULATION IN THE EVENT OF LIFE-THREATENING BLEEDING OR EMERGENT SURGERY REFERENCES

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NCCN Guidelines Version 1.2020
Perioperative Management of Anticoagulation and Antithrombotic Therapy

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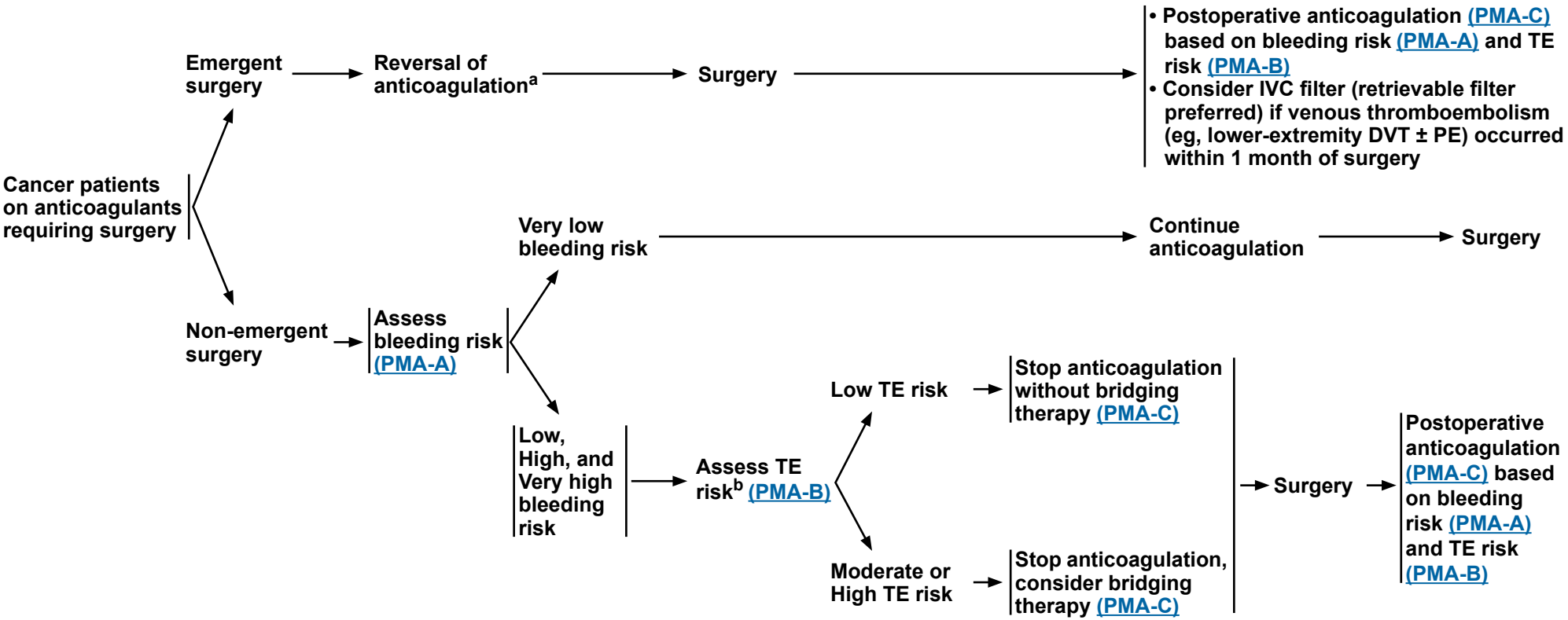

[a] See Reversal of Anticoagulation in the Event of Life-Threatening Bleeding or Emergent Surgery (VTE-L).

[b] 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.

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BLEEDING RISK ASSESSMENT TABLES

Estimated Bleeding Risk of Various Surgical Procedures

Bleeding Risk Category	Type of Surgery or Procedure	
Very high	• Neurosurgical procedure (intracranial or spinal) • Urologic surgery • Cardiac surgery	
High	• Major cancer surgery • Major vascular surgery (abdominal aortic aneurysm [AAA] repair, peripheral artery bypass) • Reconstructive plastic surgery • Renal or hepatic biopsy	• Bowel polypectomy (if part of a colonoscopy) • Major orthopedic surgery • Head and neck surgery • Major intra-abdominal surgery • Major intra-thoracic surgery
Low	• Pacemaker or automatic implantable cardioverter defibrillator (AICD) placement • Laparoscopic cholecystectomy or hernia repair • Coronary angiography • Arthroscopy • Biopsy (prostate, bladder, thyroid, lymph node)	• Bronchoscopy ± biopsy • Central venous catheter placement and removal • GI endoscopy with biopsy
Very low	• Minor dermatologic procedures (excisions of basal and squamous cell carcinomas, actinic keratoses, and malignant or premalignant nevi) • Cataract removal • Electroconvulsive therapy (ECT)	• Arthrocentesis • Joint or soft tissue injections • GI endoscopy without biopsy

Estimated Bleeding Risk of Various Dental Procedures[1]

	Low Bleeding Risk	Moderate Bleeding Risk	High Bleeding Risk
Procedures	• Supragingival scaling (standard cleaning) • Simple restorations • Local anesthetic injections • Follow recommendations for very low risk surgical procedures (See PMA-C)	• Subgingival scaling • Restorations with subgingival preparations • Standard root canal therapy • Simple extractions • Regional injection of local anesthetics • Follow recommendations for very low risk surgical procedures (See PMA-C)	• Extensive surgery • Apicoectomy (root removal) • Alveolar surgery (bone removal) • Multiple extractions • Follow recommendations for low risk surgical procedures (See PMA-C)
Suggestions	• Do not interrupt warfarin therapy • Use local measures to control bleeding[2]	• Interruption of warfarin therapy is not necessary • Use local measures to prevent or control bleeding[2] • Consult with dentist to determine comfort with use of local measures to prevent bleeding when anticoagulation is not interrupted	• May need to reduce INR or return to normal hemostasis • Use local methods to prevent or control bleeding[2]

[1] ©2017 University of Washington. Reproduced and used with permission from Suggestions for anticoagulation management before and after dental procedures. Available at: http://depts.washington.edu/anticoag/home/content/suggestions-anticoagulation-management-and-after-dental-procedures. Accessed June 23, 2017.

[2] For local measures to prevent or control bleeding, including the use of a hemostatic agent such as aminocaproic acid 5% mouth rinse, see http://depts.washington.edu/anticoag/home/content/local-methods-prevent-or-control-bleeding. Always discuss anticoagulation plan with the dentist/oral surgeon well in advance of the procedure.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

THROMBOEMBOLIC RISK ASSESSMENT FOR ARTERIAL AND VENOUS THROMBOEMBOLISM[1]

Assessing Thromboembolic Risk in the Periprocedural Period			
TE Risk Category	**Event Rate[2]**	**Arterial Thrombosis Risk Factors in Patients with Atrial Fibrillation[3] or Mechanical Heart Valves**	**Venous Thrombosis Risk Factors[4]**
High risk	**>10% per year**	• Mitral valve prosthesis • Caged ball (Starr-Edwards) or tilting disc (Bjork-Shiley) aortic valve prosthesis • Stroke or TIA within 6 months • $CHADS_2$ score 5–6	• DVT or PE within 3 months • History of recurrent VTE during subtherapeutic anticoagulation
Moderate risk	**5%–10% per year**	• Bileaflet aortic valve prosthesis plus: ▸ Atrial fibrillation ▸ Prior stroke ▸ Prior TIA ▸ Hypertension ▸ Diabetes ▸ Congestive heart failure (CHF) ▸ Age ≥75 years ▸ $CHADS_2$ score 3–4	• DVT or PE within 3 to 12 months • Recurrent DVT or PE • Active cancer or cancer treatment within 6 months
Low risk	**<5% per year**	• Bileaflet aortic valve prosthesis and no other risk factors for stroke • $CHADS_2$ score 0–2	• Single VTE event >12 months prior and no other risk factors

[1] Modified with permission from Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e326S-e350S.
[2] Event rates may be higher in cancer patients.
[3] The CHADS2 scoring system was developed in atrial fibrillation patients without cancer. It may not be valid in cancer patients. 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. The impact of these risk factors on the overall TE risk category should be assessed on a case-by-case basis in cancer patients.
[4] Patients with prior TE may have additional VTE risk factors associated with thrombophilia, including: deficiencies in protein C, protein S, or antithrombin; gene mutations in factor V Leiden or prothrombin; or antiphospholipid syndrome. The impact of these risk factors on the overall TE risk category should be assessed on a case-by-case basis.

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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINES

- **These guidelines are meant to supplement but should not supersede clinical judgment. Careful attention to each patient's individual clinical situation is the best guide to management. In general, we prefer to postpone reinitiation of irreversible anticoagulants such as apixaban, edoxaban, fondaparinux, and rivaroxaban until after tolerance with more reversible forms of anticoagulation has been established.**
- **Published clinical data supporting these recommendations are limited, particularly for patients with active cancer.**
- **Medical intervention may alter choice of postoperative anticoagulant.**
- **When designing a perioperative bridging plan it is essential for the responsible provider to communicate the plan to the patient and the procedural team (ie, surgeon and anesthesiologist) and ensure that all parties are in agreement with the plan before proceeding.**
- **For recommendations for apixaban, dabigatran, edoxaban, fondaparinux, and rivaroxaban, see PMA-C, 3 of 8.**

Warfarin Management in the Periprocedural Setting

- **For very low bleed risk, any TE risk category: Continue warfarin therapy through hospitalization and/or procedure:**
  - **Adjust dose based on target INR**
- **For all other bleed risk categories, use the pre- and post-procedure protocols. See PMA-C, 2 of 8.**

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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINES

Warfarin Management in the Periprocedural Setting

Pre-procedure Protocol

1. Stop warfarin prior to procedure, with stopping times shown in the table:

Bleeding Risk Category		
Low	High	Very High
5 d	5–7 d	7 d

2. Begin "bridge" therapy 2 days after discontinuing warfarin, per the "Bridge" dosing options shown in the table:

TE Risk	Low	No bridging necessary; if INR is >1.5 1–2 d prior to the invasive procedure, give vitamin K 1–2.5 mg orally
	Moderate	Consider bridging: LMWH prophylactic or therapeutic dose (therapeutic preferred for valves and atrial fibrillation)
	High	LMWH therapeutic dose or UFH therapeutic-adjusted IV

3. Stop LMWH/UFH "bridge" prior to procedure, with stopping times shown in the table:

Bridging Agent	Elimination Half-life	Dose	Bleeding Risk Category	
			Low	High or Very High
Dalteparin	5 h	Prophylactic	12 h	24 h
		Therapeutic[1]	24 h	48 h
Enoxaparin	7 h	Prophylactic	12 h	24 h
		Therapeutic[2]	24 h	48 h
UFH	~1 h	Therapeutic-adjusted IV	6 h	

Post-procedure Protocol

1. Consider starting UFH/LMWH prophylaxis dosing, with start times (from time of procedure) shown in the table:

Bleeding Risk Category	
Low	High or Very High
12–24 h	24 h

2. If prophylactic dose tolerated, can escalate UFH/LMWH to therapeutic dose no sooner than earliest start times (from time of procedeure) shown in the table:

		Bleed Risk		
		Low	High	Very High
TE Risk	Low	N/A (dose escalation not recommended)		
	Moderate or High	24–48 h	48–72 h	72 h

3. Restart maintenance dose of warfarin once normal diet resumes but no sooner than earliest start times (from time of procedure) shown in the table:

Bleeding Risk Category		
Low	High	Very High
24–48 h	48–72 h	72 h

[1] If once-daily therapeutic dose enoxaparin (1.5 mg/kg) is used, the last dose should be 1 mg/kg.
[2] If once-daily therapeutic dose dalteparin is used, the last dose should be half the total daily dose.

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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINE

Management of Apixaban, Dabigatran, Edoxaban, Fondaparinux, or Rivaroxaban in the Periprocedural Setting

- **For very low bleed risk, any TE risk category: Continue apixaban, dabigatran, edoxaban, or rivaroxaban therapy through hospitalization and/or procedure.**
- **For all other bleed risk categories, use the pre- and post-procedure protocols below:**

Elimination Half-life and Estimated Residual Drug Concentration

Number of Half-lives	Percent of Dose[1]
1	50%
2	25%
3	12.5%
4	6.25%
5	3.125%
6	1.6%
7	0.8%

[1]Percent of maximum drug concentration in serum.

- **For each of the pre-procedure protocols below, anticoagulant is stopped prior to procedure, with stopping time based on the terminal elimination half-life of the agent times the number of half-lives shown in the table below:**

Bleed Risk	Low			High or Very High		
TE Risk	Low	Moderate	High	Low	Moderate	High
Number of half-lives	4	4	4	6	6	6

- **Half-lives for each agent depend on patient characteristics, as shown in the tables for each agent.**

For recommendations for apixaban see PMA-C, 4 of 8, dabigatran see PMA-C, 5 of 8, edoxaban see PMA-C, 6 of 8, fondaparinux see PMA-C, 7 of 8, and rivaroxaban see PMA-C, 8 of 8.

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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINE

Apixaban Management in the Periprocedural Setting

Pre-procedure Protocol

1. Stop apixaban prior to procedure, according to the stopping times in the table:

Patient Characteristics	Terminal Elimination Half-life	Stop Apixaban Before Low Bleeding Risk Procedure	Stop Apixaban Before High/Very High Bleeding Risk Procedure
Male age 18–45 y	10–15 h	40–60 h (1.7–2.5 d)	60–90 h (2.5–3.8 d)
Female or elderly male (age >65 y)	14–16 h	56–64 h (2.3–2.7 d)	84–96 h (3.5–4 d)
Patients with moderate/severe renal impairment, CrCl 15–50 mL/min	17–18 h	68–72 h (2.8–3 d)	102–108 h (4.25–4.5 d)

2. Pre-procedural LMWH/UFH bridge
- **No need for a LMWH/UFH bridge for most patients except those patients at high risk.**
- **If bridging anticoagulation is used it will be important to consider the clearance of LMWH in patients with impaired renal function.**

Post-procedure Protocol

	Bleed Risk	
	Low	High or Very High
1. Consider starting UFH/LMWH prophylaxis dosing at:	12–24 h	24 h
2. If prophylactic dose tolerated, restart therapeutic LMWH/UFH[3] no sooner than:	48 h	72 h
3. Restart apixaban no sooner than:	72 h	7 d

[3] When transitioning to therapeutic anticoagulation in patients at high risk or very high risk for bleeding, providers may want to consider initial use of therapeutic UFH or LMWH due to their short half-lives and availability of an antidote prior to initiation of apixaban therapy.

Note: All recommendations are category 2A unless otherwise indicated.
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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINE

Dabigatran Management in the Periprocedural Setting

Pre-procedure Protocol

1. Stop dabigatran prior to procedure, according to the stopping times in the table:

Patient Characteristics	Terminal Elimination Half-life	Stop Dabigatran Before Low Bleeding Risk Procedure	Stop Dabigatran Before High/ Very High Bleeding Risk Procedure
Normal renal and hepatic function	12–17 h	48–68 h (2–2.8 d)	72–102 h (3–4.3 d)
Patients with renal impairment, rCl:			
50–80 mL/min	14–19 h	56–76 h (2.3–3.2 d)	84–114 h (3.5–4.8 d)
30–50 mL/min	17–22 h	68–88 h (2.8–3.7 d)	102–132 h (4.3–5.5 d)
15–30 mL/min	26–31 h	104–124 h (4.3–5.2 d)	156–186 h (6.5–7.8 d)

2. Pre-procedural LMWH/UFH bridge

- **No need for a LMWH/UFH bridge for most patients except those patients at high risk.**
- **If bridging anticoagulation is used it will be important to consider the clearance of LMWH in patients with impaired renal function.**

Post-procedure Protocol

	Bleed Risk	
	Low	High or Very High
1. Consider starting UFH/LMWH prophylaxis dosing at:	12–24 h	24 h
2. If prophylactic dose tolerated, can restart dabigatran[4] no sooner than:	48 h	72 h

[4] When transitioning to therapeutic anticoagulation in patients at high risk or very high risk for bleeding, providers may want to consider initial use of therapeutic UFH or LMWH due to their short half-lives prior to initiation of dabigatran therapy.

Note: All recommendations are category 2A unless otherwise indicated.
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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINE

Edoxaban Management in the Periprocedural Setting

Pre-procedure Protocol

1. Stop edoxaban prior to procedure, according to the stopping times in the table:

Patient Characteristics	Terminal Elimination Half-life	Stop Edoxaban Before Low Bleeding Risk Procedure	Stop Edoxaban Before High/Very High Bleeding Risk Procedure
All patients[5]	10–14 h	40–56 h (1.7–2.3 d)	60–84 h (2.5–3.5 d)

2. Pre-procedural LMWH/UFH bridge

- **No need for a LMWH/UFH bridge for most patients except those patients at high risk.**
- **If bridging anticoagulation is used it will be important to consider the clearance of LMWH in patients with impaired renal function.**

Post-procedure Protocol

	Bleed Risk	
	Low	High or Very High
1. Consider starting UFH/LMWH prophylaxis dosing at:	12–24 h	24 h
2. If prophylactic dose tolerated, can restart therapeutic LMWH/UFH[6] no sooner than:	48 h	72 h
3. Restart edoxaban no sooner than:	72 h	7 d

[5] Unsufficient half-life data available for patients who are female, elderly (age >65 y), or have renal insufficiency.
[6] When transitioning to therapeutic anticoagulation in patients at high risk or very high risk for bleeding, providers may want to consider initial use of therapeutic UFH or LMWH due to their short half-lives prior to initiation of edoxaban therapy.

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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINE

Fondaparinux Management in the Periprocedural Setting

Pre-procedure Protocol

1. Stop fondaparinux prior to procedure, according to the stopping times in the table:

Patient Characteristics	Terminal Elimination Half-life	Stop Fondaparinux Before Low Bleeding Risk Procedure	Stop Fondaparinux Before High/Very High Bleeding Risk Procedure
All patients[7]	17–21 h	68–84 h (2.8–3.5 d)	102–126 h (4.3–5.3 d)

2. Pre-procedural LMWH/UFH bridge
- **No need for a LMWH/UFH bridge for most patients except those patients at high risk.**
- **If bridging anticoagulation is used it will be important to consider the clearance of LMWH in patients with impaired renal function.**

Post-procedure Protocol

	Bleed Risk	
	Low	High or Very High
1. Consider starting UFH/LMWH prophylaxis dosing at:	12–24 h	24 h
2. If prophylactic dose tolerated, can restart therapeutic LMWH/UFH[8] no sooner than:	48 h	72 h
3. Restart fondaparinux no sooner than:	72 h	7 d

[7] For elderly (age ≥60 y), half-life is likely to be at the higher end of the range (ie, 21 h). Renal dysfunction has also been shown to increase half-life.
[8] When transitioning to therapeutic anticoagulation in patients at high risk or very high risk for bleeding, providers may want to consider initial use of therapeutic UFH or LMWH due to their short half-lives prior to initiation of fondaparinux therapy.

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PERIOPERATIVE ANTICOAGULATION MANAGEMENT GUIDELINE

Rivaroxaban Management in the Periprocedural Setting

Pre-procedure Protocol

1. Stop rivaroxaban prior to procedure, according to the stopping times in the table:

Patient Characteristics	Terminal Elimination Half-life	Stop Rivaroxaban Before Low Bleeding Risk Procedure	Stop Rivaroxaban Before High/Very High Bleeding Risk Procedure
Normal renal and hepatic function:			
• Male, not elderly (age <60 y)	5–9 h	20–36 h (0.8–1.5 d)	30–54 h (1.5–2.3 d)
• Female (any age ≥18 y) or elderly male (age 60–76 y)	11–13 h	44–52 h (1.8–2.2 d)	66–78 h (2.8–3.3 d)
Mild/moderate/severe renal impairment (CrCl <80 mL/min) or Mild/moderate hepatic impairment (Child-Pugh A/B):			
• Male, not elderly (age <60 y)	7–11 h	28–44 h (1.2–1.8 d)	42–66 h (1.8–2.8 d)
• Female (any age ≥18 y) or elderly male (age 60–76 y)	13–15 h	52–60 h (2.2–2.5 d)	78–90 h (3.3–3.8 d)

2. Pre-procedural LMWH/UFH bridge
- **No need for a LMWH/UFH bridge for most patients except those patients at high risk.**
- **If bridging anticoagulation is used it will be important to consider the clearance of LMWH in patients with impaired renal function.**

Post-procedure Protocol

	Bleed Risk	
	Low	High or Very High
1. Consider starting UFH/LMWH prophylaxis dosing at:	12–24 h	24 h
2. If prophylactic dose tolerated, can restart therapeutic LMWH/UFH[9] no sooner than:	48 h	72 h
3. Restart rivaroxaban no sooner than:	72 h	7 d

[9] When transitioning to therapeutic anticoagulation in patients at high risk or very high risk for bleeding, providers may want to consider initial use of therapeutic UFH or LMWH due to their short half-lives prior to initiation of rivaroxaban therapy.

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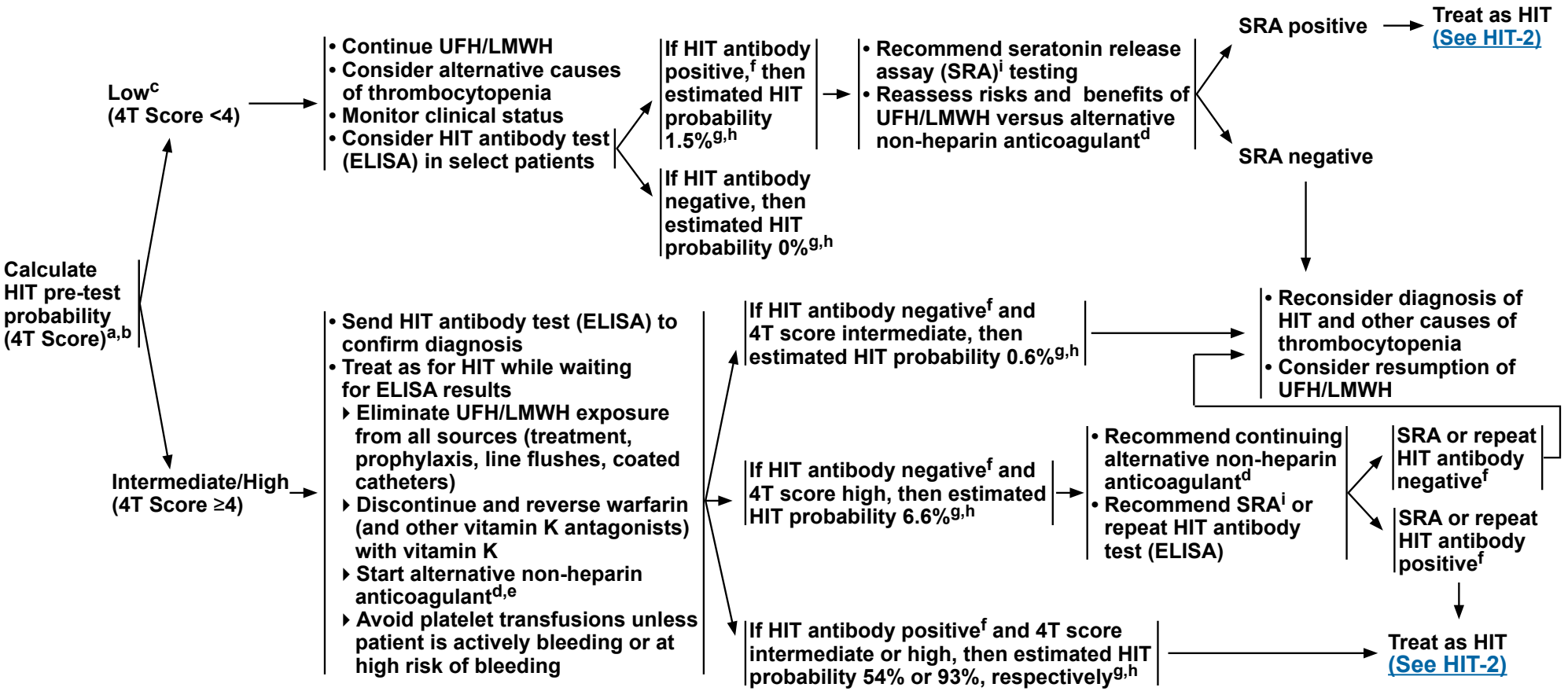
WORKUP AND MANAGEMENT FOR SUSPECTED HIT



[a] See HIT Pre-Test Probability Score Assessment (HIT-A).
[b] 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.
[c] 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 non-cancer patients 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 a DTI or fondaparinux in place of UFH/LMWH may be warranted in select patients.
[d] See Initial Treatment for Suspected or Confirmed HIT (HIT-2).
[e] 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.)
[f] Cutoff for ELISA HIT antibody test may vary depending on the specific assay used.
[g] Cuker A. Blood 2016;127:522-524.
[h] Nagler M, et al. Blood 2016;127:546-557.
[i] Consider institution-specific ELISA OD value thresholds when determining whether to send SRA.

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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 intravenous 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 direct oral anticoagulants (DOACs).[j]**
  - **DOACs or fondaparinux are considered reasonable options for the initial treatment of clinically stable patients without hemodynamically unstable pulmonary embolism or limb-threatening thrombosis or planned invasive procedures who do not have contraindications to the use of these agents as listed on VTE-E, 3 of 4.[k]**
  - **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 oral agent:**
  - **DOACs (preferred): For patients with adequate renal and hepatic function and no other contraindications (listed on VTE-E, 2 of 4).**
  - **Fondaparinux**
  - **Warfarin**
  - **For more information on agent selection and administration, see Therapeutic Options for HIT (HIT-B).**
- **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**

[j] Opinions vary among panel members regarding the quality of data supporting treatment options for the management of HIT in patients with cancer.
[k] 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 aren't equally effective. Due to the lack of data, caution is recommended when using DOACs for management of HIT in patients with cancer.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Heparin-Induced Thrombocytopenia (HIT)

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Discussion

HIT PRE-TEST PROBABILITY SCORE ASSESSMENT[1]

Suspicion of HIT based on the "4 T's"	Score	HIT Pre-test Probability Score Criteria 2	1	0
Thrombocytopenia	☐	Nadir 20,000–100,000/mcL or >50% platelet fall	Nadir 10,000–19,000/mcL or 30%–50% platelet fall	Nadir <10,000/mcL or <30% platelet fall
Timing of onset platelet fall (days of heparin therapy)	☐	Days 5–10 or ≤ day 1 with recent heparin[2]	> day 10 or timing unclear (but fits with HIT)	≤ day 1 (no recent heparin)
Thrombosis or other sequelae	☐	Proven thrombosis, skin necrosis, or ASR[3]	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
OTher cause of platelet fall	☐	None evident	Possible	Definite
Total Pre-test Probability Score	☐	Periodic reassessment as new information can change pre-test probability (eg, positive blood cultures)		

Total HIT Pre-test Probability Score

[1] Modified with permission from Warkentin TEW, Aird C, and Rand JH. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2003;497-519.
[2] Recent heparin indicates exposure within the past 30 days (2 points) or past 30–100 days (1 point).
[3] Acute systemic reaction (ASR) following IV heparin bolus.

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THERAPEUTIC OPTIONS FOR HIT[4]

Direct Oral Anticoagulants (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 no contraindications (listed on VTE-E, 3 of 4). 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 the DOAC at the same time.
  - For patients transitioning from fondaparinux to DOAC: Give the first dose of the DOAC instead of fondaparinux at the next scheduled administration time for fondaparinux.

Indirect Factor Xa Inhibitor[5]
- 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[6]
  - For patients with CrCl <30 mL/min: Avoid
  - 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

Direct Thrombin Inhibitors (DTIs)
- Argatroban (half-life 45 min with normal liver function; aPTT 1.5–3x initial baseline value not to exceed 100 sec)[7]
  - Normal liver function, non-ICU patient: 2 mcg/kg/min adjusted to aPTT ratio (first check in 4 h)
  - Abnormal liver function (total bilirubin 1.8–3.6 mg/dL; aspartate transaminase/alanine transaminase [AST/ALT] 150–600 IU/L) or ICU, heart, or multi-organ failure patient: 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)[8,9]
  - 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/mcL.

Warfarin
- Initiate once platelets ≥150,000/mcL 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 (approx 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 5–7 days overlap and when the INR reaches intended target range (≥2).
- INR and aPTT should be repeated within 2–6 hours after DTI has been discontinued to ensure the INR is still therapeutic when the effects of the 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.

[4] 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.
[5] Used as a second-line agent. Fondaparinux has been rarely associated with HIT.
[6] Prescribing Information: Fondaparinux sodium, solution for subcutaneous injection. 2009.
[7] Prescribing information: Argatroban injection, for intravenous infusion only. 2016; Lewis BE, Wallis DE, Leya F, et al. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 2003;163:1849-1856.
[8] Anaphylaxis has occurred with bivalirudin.
[9] 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;12:19044-1053.

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Guidelines Version 1.2020
Cancer-Associated Venous Thromboembolic Disease

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/17/14

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Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in cancer patients.[1,2] Results from a retrospective study of hospitalized adult cancer patients with neutropenia (n=66,106) showed that approximately 3% to 12% of these patients, depending on the type of malignancy, experienced VTE during their first hospitalization.[1] In a recent health claims database analysis of patients undergoing chemotherapy for solid tumors in the ambulatory setting (n=17,284), VTE occurred in 12.6% of patients during the 12-month period from initiation of chemotherapy.[3] The incidence ranged from 8% to 19% depending on the tumor type. VTE incidence was 1.4% among age- and gender-matched control cohort without cancer.[3] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for VTE specifically outline strategies to prevent and treat VTE in adult patients with either a diagnosis of cancer or for whom cancer is clinically suspected. These guidelines are characterized by iterative evaluations of the therapeutic advantages of implementing pharmacologic anticoagulation measures based on both the perceived risk of bleeding (ie, contraindications to anticoagulation) and the cancer status of the patient.

In the NCCN Guidelines for VTE, we define VTE broadly to include deep venous thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT), and thrombosis in other vascular territories (eg, portal vein, mesenteric vein, inferior vena cava [IVC] and superior vena cava [SVC], pelvis). DVT management is divided into categories that include the upper extremity and the SVC; the lower extremity including the IVC, pelvis, iliac, femoral, and popliteal veins; the distal lower extremity (eg, calf); the splanchnic vasculature; and catheter-related DVT.

The association of VTE with underlying malignancy was first reported by Armand Trousseau in 1865 and is supported by the results of more recent studies.[4,5] Pathophysiologic explanations of the etiology of VTE in cancer include known hypercoagulability (eg, pro-coagulants such as tissue factor expressed by cancer cells), vessel wall damage, and vessel stasis from direct compression.[6-8] The incidence of cancer-associated VTE is further increased by the presence of additional risk factors, such as acquired or congenital thrombophilia (eg, antiphospholipid syndrome, factor V Leiden), prolonged immobilization, surgical procedures, and chemotherapeutic regimens.[7,9]

The occurrence of VTE has been reported to increase the likelihood of death for cancer patients by 2- to 6-fold.[10-14] For example, gynecologic cancer patients with PE were found to have a 6-fold increased risk for death at 2 years compared with similar patients without PE.[13] Furthermore, VTE has been reported to be the most common cause of death at 30-day follow-up among cancer patients undergoing surgery.[15]

The critical need for the development of clinical practice guidelines focusing specifically on VTE in cancer patients is further underscored by the results of practice surveys of VTE prophylaxis. 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 their cancer patients.[16] Similar results were documented in the multinational IMPROVE and ENDORSE registries of hospitalized medically ill patients in which only 45% of cancer patients received any form of VTE prophylaxis.[17,18] These results are of particular concern when juxtaposed with a recent review of postmortem reports that showed that approximately 80% of cases of fatal PE occur in nonsurgical patients.[19]

VTE Risk Assessment in Patients with Cancer

Many of the risk factors for development of VTE are common to patients with cancer.[20,21] VTE risk factors in cancer patients can be grouped into 3 general categories: intrinsic and extrinsic patient-related factors, cancer-

related factors, and treatment-related factors. The VTE risk factors in the individual cancer patient are likely to be represented by all 3 risk factor categories, and the VTE risk conferred by a single risk factor cannot be evaluated in isolation from the others.

Patient-related Factors

More advanced age, a common characteristic of many cancer patients, was shown to be associated with an increased risk for VTE in some clinical settings.[1,15,22,23] In addition, obesity has been identified as a risk factor for VTE.[22,24-26] There is also evidence that pre-chemotherapy thrombocytosis,[26-28] leukocytosis,[26] and hemoglobin level <10 g/dL[26,27] are predictive of VTE in patients receiving chemotherapy, although the association of anemia with VTE may be complicated by use of erythropoietic stimulating agents (ESAs). Acquired risk factors for VTE include a history of VTE and certain hypercoagulable conditions, such as pregnancy. A history of prior VTE has been identified in a number of studies as an independent risk factor for developing a subsequent VTE.[15,25,28-31] Moreover, recurrent VTE was found to be more common among patients with cancer; for example, 12-month cumulative incidences of recurrent VTE of 20.7% and 6.8% were reported for patients with and without cancer, respectively, undergoing anticoagulant treatment.[32] Although factor V Leiden and prothrombin mutations were identified in 3.7% and 2.6%, respectively, of patients with breast or colon cancer receiving adjuvant chemotherapy in a recent prospective observational study, these inherited risk factors were not associated with an increased risk for VTE among cancer patients.[28]

A number of other patient-related VTE risk factors, although not exclusive to cancer patients, are commonly found. These risk factors include hospitalization, other medical comorbidities, such as infection, poor performance status, and prolonged immobilization.[4] In the latest report from the U.S. Centers for Disease Control and Prevention (CDC),[23] VTE events were found to occur at a high rate among hospitalized patients. Among hospitalized adults, VTE was reported in more than 547,000 patients annually (annual rate of 239 per 100,000 persons hospitalized), with more than 28,700 deaths annually in these patients.[23] The risk for VTE increased with age in hospitalized patients. 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. Infection has also been identified as an important risk factor for VTE, including in patients with cancer.[33,34] A recently published case-crossover study in individuals (≥51 years of age) hospitalized for VTE (n=399 among n=16,781 participating in the Health and Retirement Study) reported that infections, use of ESAs, blood transfusions, major surgeries, fractures, immobility, and chemotherapy were significant risk factors for VTE hospitalization.[33] In the subgroup of patients with cancer from this study, the major predictors of VTE hospitalization were infections, blood transfusions, and insertion of a central catheter.[33] In a recent population-based case-control study in patients with hospital-diagnosed VTE (n=15,009), the estimated incidence rate for VTE was increased by 3-fold among patients within the first 3 months after infection, compared with those without an infectious event during the year before VTE (incidence rate ratio=3.3 after adjustment for other VTE risk factors).[34]

Cancer-related Factors

Several VTE risk factors are exclusive to cancer patients, including the presence of malignancy, chemotherapy, and extrinsic vascular compression due to cancer-associated regional bulky lymphadenopathy. Results from 2 population-based case-control studies showed that the presence of cancer increased the risk for VTE by 4- and 7-fold.[35,36] An increased risk for VTE in patients with cancer has also been supported by the results of other studies.[29,37] Furthermore, researchers have reported cancer as the cause of approximately 20% of the VTE cases seen in the

community,[4] and a recent cancer diagnosis and the occurrence of advanced malignancies and distant metastases also increase VTE risk.[2,25,35,38,39] For example, Blom et al[35] reported an adjusted odds ratio of 19.8 for VTE risk in solid tumor cancer patients with distant metastases compared with patients without. In addition, tumor histology has been shown to influence the risk for VTE in patients. Several studies have evaluated the association between different types of cancer and the risk for developing a VTE.[1-3,10,35,37,40] For example, pancreatic cancer[1-3,10,37,38,40] and brain tumors[1,2,35,41-43] were associated with a high risk for VTE in a number of the studies. Adenocarcinomas appear to be associated with a higher risk than squamous cell cancers.[37] Although differences in study designs make it difficult to compare VTE rates according to 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 testis.[1,3,22,35,44] In addition, an increased risk for VTE has been observed in certain hematologic malignancies, such as lymphoma, acute leukemia, and multiple myeloma.[1,45,46] Patients with high-grade lymphoma and acute promyelocytic leukemia appear to be at higher risk than patients with other forms of lymphoma or leukemia.[45] In a study of patients with high-grade non-Hodgkin's lymphoma, disease-related venous compression was shown to be the most common cause of VTE in that population.[47]

Several factors associated with an increased risk for VTE in myeloma patients include the diagnosis of multiple myeloma itself, hyperviscosity, and treatment with thalidomide- or lenalidomide-based combination regimens (combined with high-dose dexamethasone, doxorubicin, or multiagent chemotherapy).[46] Further validation of the influence of these risk factors on VTE rates in patients with myeloma is warranted. In contrast, breast cancer was associated with a relatively low VTE risk in some studies.[1,11,48] Nevertheless, because of the relatively high prevalence of breast cancer, the occurrence of VTE in a patient with breast cancer is not uncommon.[42] Furthermore, the risk for VTE was shown to increase by 6-fold when patients with metastatic breast cancer were compared with patients with localized disease.[11]

Treatment-related Factors

Treatment-related risk factors include surgery, the presence of a central venous access device (CVAD, also known as a catheter), and administration of chemotherapy and other systemic treatments. For example, Heit et al[36] reported nearly 22-fold and 8-fold increases in risks for the development of VTE in patients hospitalized or confined to a nursing home with and without recent surgery, respectively, compared with non-institutionalized patients who had not undergone recent surgery.

A number of specific agents used in cancer treatment are associated with an increased risk for developing VTE. A detailed listing of these agents is not provided here; rather, the NCCN Guidelines describe some of the evidence for the association of 3 representative classes of cancer drugs (cytotoxic chemotherapy regimens, hormone therapy with estrogenic compounds, and antiangiogenic agents) with increased VTE risk.

The association of cytotoxic chemotherapy with the development of VTE in cancer patients has been shown in several studies.[26,27,49] For example, in one population-based case-control study, odds ratios of 6.5 and 4.1 for development of VTE were determined when cancer patients receiving chemotherapy and cancer patients not receiving chemotherapy, respectively, were compared with patients without a malignant neoplasm.[36] In another retrospective study, the annual incidence of VTE was 15% in patients with colorectal cancer treated with chemotherapeutic regimens.[9] Khorana et al have published a risk assessment model to estimate the risk for VTE in ambulatory cancer patients receiving chemotherapy.[26] This risk assessment model has been recently validated and extended by Ay and colleagues,[50] who identified D dimer and P

selectin as additional discriminatory risk factors for VTE in ambulatory cancer patients. However, these laboratory tests are not routinely measured in cancer patients, so their inclusion in routine thrombotic risk assessment should be predicated upon their validation in future studies. The risk factors identified by Khorana et al,[26] which formed the basis for the risk assessment models, set the stage for prospective, confirmatory randomized clinical trials evaluating the risks and benefits of risk-targeted VTE prophylaxis in ambulatory cancer patients receiving chemotherapy.

Increased VTE risk was shown to be associated with the use of exogenous hormonal compounds, such as selective estrogen receptor modulators (eg, tamoxifen, raloxifene) for the prevention and treatment of certain estrogen-receptor positive cancers.[51-55] Use of hormonal compounds, such as hormone replacement therapy[56,57] or oral contraceptive agents,[58-61] has also been associated with increased risk for developing VTE. Recent case-control studies and meta-analysis suggest that for combined oral contraceptives, VTE risks may be different between formulations, depending on the type of progestogen used.[60,62,63] Diethylstilbestrol phosphate used in combination with doxorubicin for the treatment of hormone-refractory prostate cancer was reported to increase VTE risk when compared with use of doxorubicin alone.[64] Evidence has been presented to support the association of immunomodulating agents that have antiangiogenic properties (eg, thalidomide in combination with doxorubicin and/or dexamethasone; lenalidomide in combination with dexamethasone) with an increased incidence of VTE when used in the treatment of multiple myeloma (see Guidelines section *Outpatient Prophylactic Therapy in Ambulatory Cancer Patients*).[46,65-70] Other agents used in supportive cancer care, such as ESAs, have also been associated with the development of VTE.[3,27,44,71] Concomitant use of erythropoietin with cancer therapies associated with the development of VTE, such as lenalidomide, may further increase VTE risk.[68]

Results from numerous studies have identified the presence of a CVAD as a risk factor for development of an upper-extremity DVT (UEDVT),[36,72-74] although discrepancies exist concerning the incidence of catheter-related DVT.[74,75] The association between catheter/device placement and the development of DVT may be the result of venous stasis and vessel injury after insertion of the CVAD[74,76,77] or infections occurring as a result of catheter placement.[77,78] Possible reasons for the reported discrepancies in the incidence of catheter-related DVT may include recent improvements in catheter materials and design and the different diagnostic strategies used in some of the studies (ie, clinical, which identifies symptomatic events, versus radiologic surveillance, which identifies symptomatic and asymptomatic events).[74,75]

Diagnosis and Evaluation of VTE in Cancer Patients

Clinical prediction models, such as the Wells criteria in combination with D-dimer testing, have proven useful in the diagnosis of VTE with comparable results to conventional radiologic imaging strategies. However, cancer patients comprised a minority of the subjects in these studies.[79,80] It is therefore unclear whether this strategy is as safe or effective in cancer patients. Although one study employing the Wells criteria and D-dimer testing in the diagnosis of VTE noted the performance of this strategy was comparable in patients with and without cancer, the number of cancer patients (in whom VTE had been excluded by testing) with symptomatic VTE during follow-up was 4-fold higher (2% vs. 0.5%). In addition, the number of false-positive D-dimer assays was 3-fold higher in cancer patients compared with non-cancer patients,[81] and results of a large prospective study of patients with suspected DVT that had been excluded on radiologic testing showed that high D-dimer levels were present in a large percentage of patients with cancer.[82] D-dimer testing is not recommended for the diagnosis of VTE in cancer patients, and further investigation/validation of D-dimer testing and clinical prediction models is

warranted before these strategies are incorporated into the diagnostic evaluation of VTE in cancer patients.

In addition to the imaging described below, the initial diagnostic evaluation of all patients with suspected VTE should include the following components: comprehensive medical history and physical examination; complete blood count (CBC) with platelet count and differential; prothrombin time (PT); activated partial thromboplastin time (aPTT); and comprehensive metabolic panel including liver and kidney function tests (see Guidelines sections on *DVT/SVT: Diagnosis* and *PE: Diagnosis*). In patients with a high suspicion of DVT or PE and without any known contraindications to anticoagulation, initiation of anticoagulation should be considered while awaiting results from imaging studies.

Diagnosis and Evaluation of DVT

Classic clinical symptoms are not present in all cases of acute DVT. These symptoms may include pain, unilateral edema and heaviness in the extremity distal to the site of the venous thrombosis, or edema in the face, neck, or supraclavicular space, or unexplained persistent cramping. In the prospective, multicenter MASTER registry of patients with VTE, the most common presenting symptoms of DVT were extremity edema, pain, and erythema observed in 80%, 75%, and 26% of patients with DVT, respectively.[83] 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. As mentioned previously, in patients with a high suspicion of DVT and without contraindications to anticoagulation, early initiation of anticoagulation should be considered while awaiting results from imaging studies.

Duplex venous ultrasonography is recommended as the preferred venous imaging method for initial diagnosis of DVT. Duplex ultrasonography allows for both an analysis of venous compressibility and Doppler imaging of venous blood flow,[84] although assessment of venous compressibility is considered to be more definitive[73,85]. Other advantageous characteristics of ultrasonography include accuracy for diagnosing symptomatic DVT in femoral and popliteal veins; noninvasive methodology; the lack of need for intravenous contrast agents; ability to be performed at the bedside; and lower cost.[84,86] It has been reported that 2 normal ultrasound examinations obtained 1 week apart exclude progressive lower-extremity DVT,[85] although these types of studies have not been performed in cancer patients. Disadvantages of ultrasonography include difficulties associated with imaging more central veins, such as large pelvic and iliac veins, the proximal subclavian vein, the IVC, and the SVC[87,88]; a lower sensitivity for diagnosing distal lower-extremity DVT and asymptomatic DVT[89]; limitations associated with bandages, casts, or pain; and results that are more operator dependent.[90]

In cases of negative or indeterminate ultrasound results following repeat venous imaging and a continued high clinical suspicion of DVT, other imaging modalities (listed in order of preference) are recommended: 1) Contrast-enhanced CT, also known as indirect CT venography, is reportedly as accurate as ultrasonography in diagnosing femoro-popliteal DVT and provides accurate imaging of the large pelvic and iliac veins, the IVC, subclavian veins, and the SVC.[86,91] However, this method requires relatively high concentrations of contrast agent; 2) MRI provides a sensitive and specific evaluation of the pelvic and iliac veins and vena cava without the need for nephrotoxic contrast agents.[86,92,93] Drawbacks to this method include higher cost, longer imaging times, and limited availability in some practice settings[92]; and 3) Standard invasive venography, once considered the gold standard for DVT diagnosis, has largely been replaced by less invasive methods.[92]

Few studies of UEDVT have been performed. Although UEDVT is frequently related to the presence of a CVAD[72,73,76,94] and associated with

device malfunction,[75] neither a clot within a catheter nor a simple fibrin sheath around a catheter represents a DVT. Ultrasonography has been reported to accurately detect a DVT in peripheral UEDVT involving the brachial, distal subclavian, and axillary veins.[73] However, in one study, only 50% of isolated flow abnormalities in the upper extremity were related to the presence of DVT.[95] A CT venogram may provide a more accurate assessment in cases of isolated flow abnormalities associated with an upper extremity.[95] CT venography or MR angiography may be needed to diagnose UEDVT located in the proximal subclavian vein, brachiocephalic vein, or the SVC.[76,77] Invasive venography for the detection of UEDVT should be performed through a peripheral vessel in the extremity, although venous access may be limited by edema.

The panel recommends that patients diagnosed with calf and UEDVT who have contraindications to anticoagulation therapy be re-evaluated for clot progression (eg, at 1 week for patients with calf DVT) after initial diagnosis. Similarly, patients with catheter-related DVT and central/proximal DVT should undergo follow-up imaging as clinically indicated. Reassessments of contraindications to anticoagulant therapy should accompany imaging evaluations.

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

Diagnosis and Evaluation of Superficial Vein Thrombosis (SVT)

A SVT is distinct from a DVT and generally does not have the same implications for morbidity and mortality as a DVT.[96,97] Nevertheless, SVT and DVT can occur simultaneously and each predisposes the patient to the other condition.[97] Few data are available on the incidence of SVT in patients with cancer; it has been estimated that the majority of SVT in the lower extremities occurs in the greater saphenous vein.[96,97] Although the clinical sequelae of SVT is generally less severe than for DVT, it is important to note that an extensive SVT in the saphenous vein can progress to involve the deep venous system at the saphenofemoral junction. Such clots can precipitate PE. Therefore, the location and extent of SVT should be evaluated by venous ultrasound if the possibility of proximal deep vein involvement exists.[97]

Diagnosis of SVT is made primarily on the basis of clinical symptoms (tenderness, erythema, and/or an indurated cord associated with a superficial vein) and a negative ultrasound finding for DVT. Progression of symptoms should be accompanied by follow-up imaging. SVT is more likely than DVT to be symptomatic, especially if occurring in the lower extremities. Peripheral catheter-related SVT, sometimes referred to as infusion thrombophlebitis, is often associated with a palpable tender cord along the course of the affected vein.[97] A key decision point in the treatment algorithm of SVT is the determination of the location of non–catheter-related SVT.

Trousseau's Syndrome

The presence of migratory thrombophlebitis in the presence of cancer should increase clinical suspicion for the presence of a relatively rare condition called Trousseau's syndrome. The clinical characteristics of Trousseau's syndrome can include warfarin resistance, thrombocytopenia, chronic disseminated intravascular coagulation, non-bacterial thrombotic (verrucous) endocarditis, and arterial emboli.[98,99] Effective treatment of thrombosis in Trousseau's syndrome requires the use of unfractionated or low-molecular-weight heparin (LMWH) or fondaparinux.

Diagnosis and Evaluation of Splanchnic Vein Thrombosis (SPVT)

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 venous segments.[100,101] Thrombotic events may occur in multiple segments (approximately 38%–50% of SPVT cases) or in isolated segments within the splanchnic vasculature, with isolated portal vein thrombosis (approximately 34%–40% of SPVT cases) being the most common amongst the latter.[101,102] Limited data are available to assess the relative prognosis of patients with SPVT according to the venous segment affected. In a large single-center retrospective analysis of patients with SPVT (n=832), the 10-year survival rate was significantly decreased among patients with thrombosis in multiple segments compared with those with thrombosis in a single/isolated segment (48% vs. 68%; $P < .001$); the 10-year survival rate for the entire cohort was 60%.[101] Moreover, the 10-year survival rate was highest among patients with isolated hepatic vein thrombosis (82%), while the lowest survival rate (63%) was reported in those with isolated portal vein thrombosis ($P = .045$ for comparison of Kaplan-Meier survival estimates across subgroups of isolated SPVT). The investigators attributed the lower survival rate of patients with portal vein thrombosis to the relatively high incidence of malignancies present in this group; in this retrospective study, the presence of malignancy was significantly associated with decreased survival for patients with SPVT, both in univariate and multivariate analyses.[101] In a separate retrospective study in patients with extrahepatic portal vein thrombosis (n=172), a concurrent diagnosis of mesenteric vein thrombosis was significantly predictive of decreased survival based on multivariate analysis; presence of cancer was also a significant independent predictor of mortality.[103] Several smaller retrospective studies have also reported on adverse outcomes for patients with mesenteric vein thrombosis, with a 30-day mortality rate of 20%.[104,105] Thromboses in the mesenteric vein can lead to intestinal infarction, which is frequently life-threatening.[104,105] In one study, intestinal infarction was present in 45% of patients diagnosed with mesenteric vein thrombosis, of which 19% were fatal.[102]

Various risk factors have been identified in the development of SPVT, including inherited thrombophilic states (ie, antithrombin deficiency, protein C deficiency, protein S deficiency, Factor V Leiden mutation, prothrombin *G20210A* mutation) and acquired risk factors such as malignancies, myeloproliferative disorders (eg, polycythemia vera, essential thrombocythemia), *JAK2V617F* mutation with or without overt myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria (PNH), abdominal surgery (eg, splenectomy), pancreatitis, and cirrhosis.[102,103,106-108] In addition, the use of exogenous estrogen, such as oral contraceptives or hormone replacement therapy, has also been linked to SPVT.[103,106,108] Patients with SPVT may have multiple risk factors, whether inherited and/or acquired. The presence of cancer itself, especially abdominal malignancies, is both a common risk factor for SPVT and a frequent cause of death in cancer patients with SPVT.[101,103,108] Several retrospective studies have reported cancer to be a significant independent predictor of mortality in patients with SPVT.[101,103-105] Moreover, among patients with cancer, the presence of SPVT has been associated with decreased survival. Portal vein thrombosis has been reported in about 20% to 30% of patients with hepatocellular carcinoma at the time of diagnosis.[109-111] In a retrospective study of patients with hepatocellular carcinoma treated at a referral center in Germany (n=389), patients with portal vein thrombosis had significantly decreased median survival (6 months) compared with patients without portal vein thrombosis (16 months); based on multivariate analysis, presence of portal vein thrombosis was a significant independent predictor of 5-year survival in this population.[110] The poor prognosis associated with SPVT in patients with hepatocellular carcinoma was demonstrated in another retrospective study (n=194), which also showed significantly decreased median survival in patients with portal vein thrombosis (2.3 months vs. 17.6 months in patients without; $P = .004$).[109]

In a recent meta-analysis of 30 randomized controlled trials in patients with previously untreated hepatocellular carcinoma receiving palliative treatments, the presence of portal vein thrombosis was identified as one of the independent predictors of decreased survival.[112]

Clinical manifestations of acute SPVT typically include abdominal pain, ascites, hepatomegaly, nausea, vomiting, anorexia, and diarrhea.[108,113-118] SPVT may also be an incidental finding. Among patients with acute thrombosis in the mesenteric vein, intestinal infarction has been reported in 30% to 45% of patients at the time of diagnosis.[102,104] Abdominal pain associated with mesenteric vein thrombosis has been described as a mid-abdominal, colicky pain.[108] Fever, guarding, and rebound tenderness may also be present, which may be indicative of progression to bowel infarction.[108] Chronic SPVT may often be asymptomatic due to formation of collateral veins,[108,113,115,119] although abdominal pain, nausea, vomiting, anorexia, lower-extremity edema, and splenomegaly have been reported with chronic presentations.[115,118] Weight loss, abdominal distension, and postprandial abdominal pain may also be associated with chronic mesenteric vein thrombosis.[119] 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.[114,115,119]

The diagnostic evaluation includes both imaging and laboratory testing. Diagnosis is confirmed by the absence of blood flow or presence of a thrombus in the splanchnic veins based on noninvasive imaging by duplex ultrasonography, CT angiography (CTA) and/or MR venography (MRV) of the abdomen. Acute SPVT is associated with presenting signs or symptoms of ≤8 weeks duration, with no portal cavernoma (cavernous transformation showing a network of collaterals around the portal vein) and no signs of portal hypertension.[116] The presence of portal cavernoma on imaging is indicative of chronic thrombosis.[114,116,120] For suspected cases of SPVT involving the hepatic and/or portal veins, duplex ultrasonography is considered the initial choice of imaging.[106,113,114,120] CTA or MRV may be useful in evaluating vascular structure, venous patency, presence of ascites, potential impairment of the bowel and other adjacent organs, and for identifying complications such as bowel ischemia.[106,119,120] For cases of SPVT involving the mesenteric veins, use of duplex ultrasonography frequently may be limited by overlying bowel gas; for suspected mesenteric vein thrombosis, CTA is the preferred method of diagnostic imaging.[106,108,119] Once a diagnosis of SPVT has been established, considerations may be given to evaluate the patient for thrombophilia or to test for PNH or the *JAK2* gene mutation. PNH is a rare acquired hematopoietic disorder resulting in chronic hemolysis, and has been associated with a high propensity for venous thrombosis particularly in the splanchnic vasculature.[121,122] PNH is an important acquired risk factor for SPVT[106,108]; in a recent *post hoc* analysis (n=77) from a study of patients with Budd-Chiari syndrome, patients who had underlying PNH more frequently presented with additional SPVT (ie, portal, mesenteric, or splenic vein thrombosis) at baseline compared with patients without PNH (47% vs. 10%; $P = .002$).[123] 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.[124-127] The presence of myeloproliferative disorders or having *JAK2V617F* mutation, with or without myeloproliferative disorders, is the most common acquired risk factor for SPVT.[106] In the absence of overt myeloproliferative disorders, *JAK2V617F* has been detected in approximately 20% to 40% of patients with SPVT.[106,128-130] Mutations in exon 12 of *JAK2* may also be associated with SPVT in patients without *JAK2V617F*.[131]

Diagnosis and Evaluation of PE

Diagnosis of PE in adults with cancer should include an increased level of clinical suspicion on presentation of any clinically overt signs or symptoms that could represent acute PE. Classic clinical signs and/or symptoms, including unexplained shortness of breath, chest pain—particularly pleuritic chest pain—tachycardia, apprehension, tachypnea, syncope, and hypoxia, are not present in all cases of acute PE. The clinical presentation of PE can range from stable hemodynamics to cardiogenic shock.[132] 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.[83]

Radiographic evidence of DVT is found in up to 50% to 70% of patients presenting with symptomatic PE and vice versa.[83,133,134] Asymptomatic patients with incidental radiographic findings of PE should be treated similarly to patients with symptomatic PE, as many have subtle clinical symptoms of active disease on further evaluation.[135] They should undergo additional workup to evaluate for PE; however, repeat imaging is not routinely needed for these patients. As mentioned previously, in patients with a high clinical suspicion of PE and without contraindications to anticoagulation, early initiation of anticoagulation should be considered while awaiting results from imaging studies.

Neither a chest radiograph nor an electrocardiogram (EKG) in a patient with suspected PE is sensitive or specific enough to diagnose PE. However, a chest radiograph facilitates the diagnosis of comorbidities and conditions with clinically similar presentations and is useful in the interpretation of a ventilation-perfusion (VQ) lung scan.[136] The EKG provides information about existing cardiac disease and PE-related changes. Furthermore, EKG patterns characteristic of right ventricular (RV) strain have been associated with PE,[137] and inverted T waves in precordial leads may be evident in cases of massive PE.[138]

The NCCN Panel recommends CTA, which allows for indirect evaluation of pulmonary vessels, as the preferred imaging technique for the initial diagnosis of PE in most patients. Advantages of this method include accurate imaging of mediastinal and parenchymal structures; accurate visualization of emboli in many regions of the pulmonary vasculature; the capability to be performed in conjunction with indirect CT venography, which can detect DVT[86,139] (since the most common cause of PE is DVT in lower extremities or pelvis[140]); and the ability to detect signs of RV enlargement, which can be used in assessing the patient's risk for adverse clinical outcomes.[141] Disadvantages of CTA include the associated radiation exposure and the need for large amounts of IV contrast, particularly when CTA is followed by indirect CT venography.[86]

Alternative imaging modalities used for the diagnosis for PE include: 1) VQ lung scan; and 2) conventional pulmonary angiography. A VQ scan is associated with less fetal radiation exposure than CTA, so it is useful for pregnant patients and patients with renal insufficiency or untreatable contrast allergies in whom IV contrast is not feasible. It is also less invasive than conventional pulmonary angiography. A normal VQ scan result essentially excludes PE.[142] In a recent non-inferiority study, 1417 patients determined to have a high risk for PE according to the Wells criteria were randomized to undergo CTA or VQ scanning. CTA identified significantly more PE than VQ scans (19.2% vs. 14.2%; 95% CI, 1.1%–8.9%).[142] Elderly patients are more likely than younger patients to be diagnosed with an intermediate probability VQ scan result.[143] Both intermediate and low-probability VQ scan results lack diagnostic utility and should be considered indeterminate. Further diagnostic testing should be performed if clinically indicated. In a patient clinically suspected to have a PE, a high-probability VQ scan is diagnostic. Conventional pulmonary angiography (direct pulmonary angiography), often considered to be the gold standard for PE diagnosis, is infrequently used today because of its invasive nature. Rarely, this method is combined with catheter-directed

thrombectomy or thrombolysis. These measures should be planned before and executed simultaneously with conventional pulmonary angiography.

Fatality due to PE primarily occurs through RV heart failure and cardiogenic shock.[132] Since the 3-month mortality rate of patients with PE has been reported to be 15%, outpatient management should be limited to individuals at low-risk for adverse outcomes.[144] The panel recommends that patients with PE be risk-stratified.[145,146] CTA or echocardiography can be used to assess PE patients for RV enlargement/dysfunction, which is associated with an increased risk for adverse clinical outcomes.[132,141,144,147-150] Elevated serum troponin levels, which are released due to endomyocardial damage, have also been associated with adverse clinical outcomes[132,147,151,152] as has the presence of residual DVT on lower-extremity duplex imaging.[153] A recent study demonstrated that combining the results from at least 2 of the above tests (ie, serum troponin measurement, echocardiography for detecting RV dysfunction, lower-extremity ultrasonography for detecting DVT) 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.[145]

A clinical risk assessment tool–the Pulmonary Embolism Severity Index (PESI)–has also been used to assess the advisability of outpatient management and intensity of initial follow-up and treatment. The PESI score is a validated patient assessment rule that includes age, sex, a history of heart or lung disease, a history of cancer, and physiologic signs associated with PE that can be used to determine a patient's risk for an adverse outcome associated with PE.[154,155] Another stratification tool, known as the RIETE (Computerized Registry of Patients with Venous Thromboembolism) Cancer Score, has been developed to identify individuals at low-risk of mortality from PE and validated in the cancer population.[156] The NCCN Panel recommends that upon diagnosis, all cancer patients with PE be considered for risk stratification with a combination of imaging modalities (CTA or transthoracic echocardiogram to assess RV enlargement or dysfunction) plus serum troponin measurement.[145,146] The PESI or RIETE score can be included as an adjunctive risk assessment tool, but should not be substituted for the above risk-stratification procedures until validation studies are conducted in patients with cancer.

Anticoagulation in Cancer Patients: Contraindications and Risks

Contraindications to 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 in the individual patient (see Guidelines section *Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment*). Absolute contraindications to anticoagulation include recent central nervous system bleeding, the presence of intracranial or spinal lesions at high risk of bleeding, and major active bleeding requiring >2 units of blood transfusions in 24 hours. Relative contraindications, for which the risks and benefits of anticoagulation must be considered on an individual basis, include: 1) chronic, clinically significant bleeding (for >48 hours); 2) recent major surgery associated with a high risk of bleeding; 3) high risk for falls and/or head trauma; 4) thrombocytopenia (platelets <50,000/mcL); 5) severe platelet dysfunction (eg, due to uremia, medications, dysplastic hematopoiesis); 6) underlying hemorrhagic coagulopathy; and 7) neuraxial anesthesia or lumbar puncture. Timing is of concern when using LMWH in the setting of neuraxial procedures. Placement or removal of a neuraxial catheter should be delayed for at least 12 hours after administration of prophylactic doses of anticoagulation. Longer delays of up to 24 hours are appropriate to consider for patients receiving therapeutic doses of LMWH. A postprocedure dose of LMWH should usually be given no sooner than 4

hours after catheter removal. The panel recommends frequent re-evaluation of these contraindications and of the risks and benefits of anticoagulation therapy for any cancer patient considered to be at increased risk of bleeding.

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 all 3 of the 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.[157-160] Unfractionated heparin (UFH) should also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture.[161] Other factors, such as a patient's risk of falling, should also be considered before anticoagulation therapy is ordered.

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 antiphospholipid syndrome. Antiphospholipid antibodies prolong the aPTT by interfering with the interaction of coagulation factors in the patient plasma sample with 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.[162-164] Any patient who has experienced a thrombotic event and fulfills diagnostic criteria for antiphospholipid syndrome should be considered for indefinite anticoagulation therapy.[163]

Risks Associated with Anticoagulation Therapy

The use of anticoagulants in cancer patients is complicated by the fact that these patients have higher risks of both recurrent VTE and bleeding.[32,165,166] In one prospective follow-up study of patients undergoing anticoagulation therapy for VTE, the 12-month cumulative incidence of major bleeding was 12.4% and 4.9% in patients with and without cancer, respectively (hazard ratio, 2.2; 95% CI, 1.2–4.1).[32] In this study, one-third of all cases of major bleeding occurred during the initial 5 to 10 days of heparinization, and the risk of bleeding increased with the extent of cancer. In contrast to patients without cancer, cancer patients remain at increased risk of bleeding during vitamin K antagonist therapy regardless of International Normalized Ratio (INR) level.[32,165,166] These findings suggest that factors other than the intensity of anticoagulation, such as thrombocytopenia and organ or vascular invasion by tumors, are responsible for increased bleeding in cancer patients. Subsequent randomized controlled studies of LMWHs and vitamin K antagonists in the chronic treatment of VTE in cancer patients have demonstrated that LMWH is associated with a similar incidence of bleeding events, including major bleeding[167-169]; however, in one study, fatal bleeding within the 3-month treatment period was reported in 8% of patients receiving vitamin K antagonists compared with none receiving LMWH.[169] Other risks associated with chronic use of anticoagulants include osteoporosis and heparin-induced thrombocytopenia (HIT) for patients receiving heparins, and drug and food interactions for patients receiving oral anticoagulants. For example, in patients who underwent chronic anticoagulant therapy for 3 to 24 months with an oral anticoagulant 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.[170]

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.[171,172] Furthermore,

certain chemotherapeutic agents, such as the fluoropyrimidines (5-fluorouracil and capecitabine), are known to increase the INR in patients undergoing warfarin anticoagulation,[173,174] and drug interactions between warfarin and certain selective estrogen receptor modulators (tamoxifen and raloxifene) have also been reported.[175] Dietary intake of vitamin K and certain dietary supplements can also influence the effects of warfarin.[176,177] Finally, acetaminophen, found in many medications, can increase the therapeutic effects of warfarin when taken in daily doses exceeding 2 g.[178]

Therapies for Prophylaxis or Treatment of VTE in Cancer Patients

The only placebo-controlled, randomized clinical trial on the use of anticoagulants to treat VTE was performed in 1960.[179,180] Results from this study showed that treatment with heparin followed by warfarin dramatically reduced VTE recurrence and associated mortality in patients with symptoms of acute PE. Although most of the subsequent clinical trials 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.[181-183] Clinical evidence for the safety and efficacy of anticoagulation therapy in cancer patients is described later. It is the directive of NCCN that all adult, hospitalized patients with cancer receive anticoagulation therapy in the absence of contraindications (category 1).

Anticoagulants

Anticoagulation agents used in the prophylaxis and/or treatment of VTE are listed and described according to guideline recommendations (see Guidelines sections *Inpatient/Outpatient Prophylactic Anticoagulation Treatment*, *Therapeutic Anticoagulation Treatment for Venous Thromboembolism*, and *Therapeutic Options for Heparin-Induced Thrombocytopenia [HIT]*). U.S. Food and Drug Administration (FDA) indications and NCCN recommendations for use of each of 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). The panel recommends that agent selection be based on criteria such as the presence of renal insufficiency, FDA approval, cost, ease of administration, need for therapeutic monitoring, and ease of reversibility. Suggested dosing schedules included within this guideline were established according to the NCCN VTE Guidelines Panel consensus and follow, with several exceptions, manufacturer recommendations. To avoid potential conflicts, users can also 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.[181-183]

Low-Molecular-Weight Heparins

LMWHs, such as dalteparin and enoxaparin, are attractive agents for VTE treatment and prevention because they facilitate outpatient treatment and eliminate the need for therapeutic monitoring in most patients. Another LMWH, tinzaparin, has been discontinued in the United States. Although the 2 LMWHs are commonly considered therapeutically equivalent and are often used interchangeably, few clinical studies have tested whether the clinical effects of these agents are comparable. Furthermore, the agents differ pharmacologically with respect to mean molecular weight, half-life, and ability to inhibit thrombin and factor Xa. Enoxaparin[158] is approved by the FDA for both prophylaxis and immediate treatment of VTE, and dalteparin[160] is approved for VTE and extended treatment of symptomatic VTE in patients with cancer.

NCCN-recommended dosing regimens for dalteparin in immediate VTE treatment are based on the results of clinical studies and panel consensus (see Guidelines section on *Therapeutic Anticoagulation Treatment for*

Venous Thromboembolism).[168,184-188] Extended or chronic anticoagulation therapy with a LMWH may require dosage reduction after an initial period. For example, in the CLOT study, the dalteparin dosing was lowered from 200 units/kg every day to 150 units/kg every day after 1 month.[168] In addition, the European Society for Medical Oncology (ESMO) clinical recommendations for management of VTE in cancer patients specifies using 75% to 80% of the initial dose of LMWH for extended anticoagulation therapy.[189] Only limited evidence exists concerning the safety and efficacy of LMWHs in special populations, such as patients with renal insufficiency, patients with a body mass index (BMI) more than 30 kg/m^2, patients weighing less than 50 kg, patients aged 70 years or older, and patients with cancer.[190-192] Of the 3 LMWHs, specific dosing recommendations for patients with severe renal insufficiency (creatinine clearance [C_{cr}] <30 mL/min) are available only for enoxaparin.[158,193] Manufacturer recommendations specify 30 mg enoxaparin subcutaneously daily for VTE prophylaxis and 1 mg/kg subcutaneously every 24 hours for VTE treatment of patients with C_{cr} <30 mL/min. These recommendations are supported by results of a meta-analysis showing enoxaparin to be associated with a 2- to 3-fold increase in risk of bleeding when administered in standard, unadjusted therapeutic doses to patients with severe renal insufficiency, compared with patients without severe renal insufficiency.[194] In another study, renal clearance of enoxaparin was shown to be reduced by 31% and 44% in patients with moderate (30–60 mL/min) and severe renal impairment (<30 mL/min), respectively, leading the authors to suggest dose reductions for patients with C_{cr} values <50 mL/min.[195] Furthermore, some evidence supports downward dose adjustments of enoxaparin in the management of patients with C_{cr} of 30 to 60 mL/min.[196]

Some data are available with respect to the safety of dalteparin in patients with renal insufficiency. In a small study of patients (n=22) treated with dalteparin, mean anti-Xa activity was similar between patients with renal impairment (mean C_{cr} 26 mL/min; range, 16–38) and those with normal renal function (C_{cr} >80 mL/min).[197] In a more recent study of prophylactic dalteparin in critically ill patients (n=138 evaluable) with severe renal impairment (C_{cr} <30 mL/min), no bioaccumulation was detected after a median of 7 days of prophylactic dose dalteparin (5000 IU daily), and treatment was not associated with excessive anticoagulation; peak anti-Xa levels were between 0.29 and 0.34 IU/mL.[198] For cancer patients with C_{cr} <30 mL/min receiving dalteparin for extended treatment of acute VTE, the manufacturer recommends monitoring of peak anti-Xa levels to achieve a target range of 0.5 to 1.5 IU/mL; it is suggested that sampling for anti-Xa levels be taken 4 to 6 hours after dosing, and only after the patient has received 3 to 4 doses of dalteparin.[160]

The panel currently recommends using caution when administering LMWH to patients with severe renal insufficiency and following manufacturer specifications when administering enoxaparin to these patients.[158] The panel also recognizes current evidence suggesting caution should be used when administering LMWHs to patients with C_{cr} less than 50 mL/min. Additional studies are needed to determine the safety of LMWH in patients with compromised renal function, including patients with cancer. Concerns also exist with respect to maintaining and monitoring therapeutic concentrations of anticoagulants in obese patients. In one study, thromboprophylaxis with 5000 units of dalteparin per day was ineffective in reducing the incidence of symptomatic VTE and asymptomatic DVT in patients with a BMI of 40 kg/m^2 or greater.[199] Hospitalization of morbidly obese cancer patients with administration of UFH should be considered. The panel suggests that each institution prepare a LMWH dosing algorithm tailored for obese patients. Because only limited data are available for the use of LMWHs in patients weighing less than 50 kg,[157,158,160] the panel also recommends caution when using these agents in patients with low body weight and in elderly patients. LMWHs are contraindicated in patients with HIT, and should only be used with caution

in patients with a history of HIT. In this situation, a direct thrombin inhibitor (DTI) or fondaparinux represent safer alternatives (see Discussion section *Related Issues in VTE Prophylaxis and Treatment*). Later sections summarize the clinical evidence for the safety and efficacy of LMWHs in cancer patients (see Discussion sections *VTE Prophylaxis* and *VTE Treatment*).

Factor Xa Inhibitors

Fondaparinux is a specific Factor Xa inhibitor approved by the FDA for the prophylaxis of DVT in patients undergoing hip fracture surgery, hip or knee replacement surgery, or abdominal surgery, and treatment of DVT or acute PE when administered in conjunction with warfarin.[159] Advantages of fondaparinux in the treatment of VTE include specific neutralization of factor Xa, elimination of the need to monitor anticoagulant response in most patients, and the lack of cross reactivity with the antibody associated with HIT.[159,200-202] However, the use of fondaparinux in patient populations with renal insufficiency, obesity, or HIT has not been well defined,[192,202] although there is some evidence to support its safe and effective use for VTE prophylaxis for older patients with a broad range of body weights.[203] Pharmacologic characteristics of fondaparinux include renal elimination and a very long half-life of 17 to 21 hours.[159] Prescribing information for fondaparinux provided by the manufacturer specifies that the drug is contraindicated in patients with severe renal insufficiency (C_{cr} <30 mL/min) and for thromboprophylaxis in patients weighing less than 50 kg undergoing orthopedic or abdominal surgery.[159] It should be used with caution in elderly patients[203] and individuals with moderate renal insufficiency (C_{cr} <50 mL/min).[159] The NCCN Panel recommends against the use of fondaparinux in patients with severe renal insufficiency and advises caution when using fondaparinux in all patients weighing less than 50 kg, patients with renal dysfunction (C_{cr} 30–50 mL/min), and elderly patients (>75 years of age).

Rivaroxaban is an orally administered direct Factor Xa inhibitor approved by the FDA for the prevention of DVT, which may lead to PE, in patients undergoing hip or knee replacement surgery; it is also approved for the treatment of DVT and PE and prevention of for stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[204-206] The drug is primarily eliminated via the kidneys (66% renal excretion) with a lesser proportion cleared by hepatic metabolism (CYP450 3A4 dependent and independent mechanisms). Rivaroxaban is considered a low-clearance drug, as protein binding in plasma is high (92%–95%).[204] The half-life is 5 to 9 hours in healthy individuals aged 20 to 45 years and extends to 11 to 13 hours in elderly patients. The prescribing information for rivaroxaban provided by the manufacturer specifies that the drug should be avoided in patients with severe renal impairment (C_{cr} <30 mL/min) and should be used with caution in those with moderate impairment (C_{cr} 30–50 mL/min).[204] In randomized clinical trials, rivaroxaban has been evaluated for thromboprophylaxis in hospitalized acutely ill medical patients[207] and for chronic anticoagulation therapy for prevention of recurrent VTE in patients who experienced an initial VTE event (PE with or without DVT),[206] in comparison with the LMWH enoxaparin. Although results showed non-inferiority of rivaroxaban compared with enoxaparin, the proportion of enrolled patients with active cancer were very low (5%–6%) in these studies. Until further data become available in cancer patients, this agent is currently not recommended by the NCCN Guidelines Panel for prophylactic or therapeutic anticoagulation in patients with cancer.

Apixaban is another orally administered direct Factor Xa inhibitor recently approved by the FDA. It is currently approved for prevention of thromboembolism in patients with nonvalvular atrial fibrillation, the prevention of VTE after hip and knee arthroplasty, and the treatment of VTE.[208-211] Apixaban is primarily metabolized via the liver (CYP450 3A4 dependent); renal elimination accounts for about 27% of total drug clearance. The apparent half-life after oral administration of the drug is

about 12 hours.[208] The prescribing information for apixaban provided by the manufacturer specifies that the drug should be avoided in patients with severe hepatic impairment. Recent randomized clinical trials have evaluated the potential role of apixaban for thromboprophylaxis in hospitalized acutely ill medical patients (in comparison with the LMWH enoxaparin),[212] and for extended anticoagulation therapy in patients who completed initial anticoagulation for VTE (in comparison with placebo).[213] Apixaban (2.5 mg twice daily for 30 days) was not superior to a standard course of enoxaparin (40 mg once daily for 6–14 days) in preventing VTE in acutely ill patients, and was associated with an increased risk for major bleeding events.[212] In the randomized study involving patients who received 6 to 12 months of anticoagulation for chronic VTE management, extended treatment with apixaban was associated with a significantly decreased risk for recurrent VTE compared with placebo.[213] However, only a small percentage of patients with active cancer (1.7%) were included in this study (see Discussion section *Chronic VTE Treatment*). As in the case with rivaroxaban mentioned above, the NCCN Panel currently does not recommend apixaban for thromboprophylaxis or for the treatment of VTE due to the lack of sufficient clinical data in patients with cancer.

Unfractionated Heparin

UFH is generally administered subcutaneously for VTE prophylaxis (low-dose heparin) and by intravenous infusion for treatment of VTE.[214] Low-dose UFH (5000 units) administered 3 times/day (every 8 hours) was shown to be more effective than low-dose UFH administered twice a day in preventing DVT in general surgery patients[215] and is the regimen recommended by the panel for VTE prophylaxis in cancer patients. However, no difference in the overall rate of VTE based on the dosing of prophylactic UFH (5000 units 2 times/day vs. 3 times/day) was observed in a meta-analysis of clinical trials conducted in general medical patients, although a decrease was seen in the combined endpoint of proximal DVT and PE (P = .05) and the risk of major bleeding was significantly higher when UFH was administered 3 times daily (P < .001).[216,217]

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.[191] The safety and efficacy of fixed dose, unmonitored, subcutaneous UFH has been reported to be comparable to LMWH in the treatment of patients with acute VTE,[218] but further investigation is warranted before this regimen can be routinely used in cancer patients. Patients receiving intravenous UFH must be hospitalized and monitored for anticoagulant response. The panel recommends UFH as the agent of choice in patients with C_{cr} <30 mL/min, because the liver is a main site of heparin biotransformation.[161,200] Some exceptions include patients with severe renal dysfunction but without intravenous access and those with a new diagnosis of VTE despite therapeutic doses of UFH. UFH is contraindicated in patients with HIT and should only be used with extreme caution in patients with a history of HIT. In this situation, a DTI or fondaparinux is a better alternative (see Discussion section *Related Issues in VTE Prophylaxis and Treatment*).

Warfarin

Warfarin is an option for long-term treatment of VTE in cancer patients. If warfarin is to be used for chronic therapy, it should be administered concomitantly with UFH, LMWH, or fondaparinux for at least 5 days and until an INR of 2 or more is achieved before discontinuing the parenteral anticoagulant agent. When treating patients with HIT, warfarin should not be initiated until the platelet count has recovered and then it should be overlapped with a DTI or fondaparinux for at least 5 days and until the INR is 2 or more (see Discussion section *Related Issues in VTE Prophylaxis and Treatment*). During the transition to warfarin monotherapy, the INR should be measured at least twice weekly and then at least once every week once the patient has begun receiving warfarin monotherapy.

Warfarin can be safely administered to patients with renal insufficiency, although the response to warfarin is accentuated in patients with hepatic insufficiency.[219]

Direct Thrombin Inhibitors

DTIs are discussed in a later section (see Discussion sections *VTE Therapies: Response Assessment* and *Diagnosis and Management of HIT*).

Aspirin

Aspirin (81–325 mg daily) is an option for VTE prophylaxis in only a select group of multiple myeloma patients with one or fewer individual or multiple myeloma-specific risk factors. Aspirin is not considered to be effective VTE prophylaxis in other settings. In the Women's Health study, a 10-year study of healthy women randomly assigned to aspirin (100 mg) or placebo on alternate days, no significant differences in the incidence of VTE were observed between the 2 arms.[220] Thus, aspirin provided no benefit for initially healthy women who had no or very few risk factors for VTE. A recent double-blind, randomized, controlled study compared the efficacy and safety of aspirin (100 mg daily; n=205) versus placebo (n=197) in patients with a first unprovoked VTE who had completed 6–12 months of oral anticoagulation therapy prior to study initiation.[221,222] Study treatment was administered for at least 2 years. During the study period (median 24.6 months), VTE recurrence occurred in 14% and 22% of patients who received aspirin and placebo, respectively; this translated to a significant reduction in risk for VTE recurrence with aspirin (6.6% vs. 11.2% per year; hazard ratio, 0.58; 95% CI, 0.36–0.93).[222] The incidence of clinically relevant bleeding events was similar between study arms; major bleeding occurred in 1 patient in each study arm. Similar results were identified in the placebo-controlled randomized controlled ASPIRE study which found that low dose aspirin reduced the incidence of VTE by from 6.5% per year to 4.8% per year (HR with aspirin, 0.74; 95% CI, 0.52 to 1.05; *P* = .09). Although these studies suggested that extended therapy with aspirin following initial oral anticoagulation was beneficial in preventing VTE recurrence, these data cannot be extrapolated to cancer patients with VTE who were excluded from participation in the studies.

Mechanical Devices

Intermittent Pneumatic Compression (IPC) Device

One of the main advantages of an IPC device is the absence of an associated bleeding risk. However, disadvantages include the potential for interference with ambulation and the need to keep the devices in place nearly continuously until patients are fully ambulatory. Graduated compression stockings (GCS) can be used in conjunction with an IPC device as a method of mechanical prophylaxis.

Vena Cava Filters

Vena cava filters are indicated for prevention of PE in patients who cannot be anticoagulated due to an absolute contraindication to therapeutic anticoagulation or complications from anticoagulation.[223-227] However, placement of an IVC filter does not prevent DVT and has been associated with an increased risk for recurrent DVT.[223,228,229] A randomized controlled trial has assessed the efficacy and safety of IVC filters in conjunction with anticoagulation compared with anticoagulant therapy alone in the treatment of acute VTE. However, this pivotal trial did not test the efficacy of IVC filters in the usual clinical scenario in which they are used, in patients without concomitant anticoagulation.[223,228] It is unclear if IVC filter placement is beneficial in the absence of ilio-popliteal lower-extremity IVC or pelvic DVT.

IVC filters are available as either a retrievable ("optional") or permanent filter; however, the time period for recovery of a retrievable filter is limited.[230,231] Results from a retrospective cohort study of 702 patients with IVC filter placement showed that filter retrieval was attempted for only

15.5% of patients who received a retrievable filter, and only 70% of those attempts were successful.[232] No significant differences in PE protection or complication rates were observed between the 2 filter types, although mean follow-up time was limited to 11.5 months. A recent case series of patients who received a Bard G2 or Recovery filters noted filter strut fracture in up to 25% of recipients after a mean follow-up of 24 and 50 months, respectively.[233] It remains unclear whether the frequency of this complication is device-specific or a characteristic of all filters. Until further data are available, this experience emphasizes the importance of placing filters only in patients in whom the benefits outweigh the risks, and retrieving filters whenever possible.

VTE Prophylaxis

Prophylactic Anticoagulation Therapy

Inpatient Prophylactic Therapy

Hospitalized patients with cancer are at high risk for VTE.[1,234] The panel recommends prophylactic anticoagulation therapy for all inpatients with a diagnosis of active cancer or clinical suspicion of cancer and without contraindication to such therapy (category 1). This recommendation is based on an assumption that ambulation in hospitalized cancer patients is inadequate to reduce VTE risk. Recommended anticoagulant options for VTE prophylaxis of cancer inpatients are listed within the Guidelines section *Inpatient/Outpatient Prophylactic Anticoagulation Treatment*. The LMWHs, fondaparinux, and subcutaneous UFH (5000 units 3 times/day) are category 1 options for inpatient prophylactic therapy. Anticoagulation therapy should be administered throughout the duration of hospitalization. Adult inpatients with cancer should undergo the following evaluation prior to the initiation of thromboprophylaxis: comprehensive medical history and physical examination; CBC with platelet count and differential; PT; aPTT; and liver and kidney function tests.

Studies comparing different anticoagulant regimens for the prevention of VTE in cancer patients have not clearly identified a particular regimen to have superior efficacy. In a randomized multicenter clinical trial, no difference in VTE and bleeding rates were seen for cancer patients receiving perioperative enoxaparin (40 mg) once daily versus low-dose UFH 3 times a day to prevent VTE after major elective abdominal or pelvic surgery.[235] Furthermore, results from a meta-analysis of randomized clinical studies of general surgery patients found LMWHs to be as safe and effective as UFH in the prevention of VTE.[236] However, results from a nonrandomized historically controlled study comparing the effectiveness of the LMWH dalteparin (5000 units once daily) to low-dose UFH (5000 units 3 times/day) as VTE prophylaxis in high-risk women undergoing surgery for gynecologic cancer indicated that the dalteparin dosing regimen may not be optimal in these patients.[237] More recently, a meta-analysis comparing outcomes of perioperative VTE prophylaxis with LMWH versus UFH in cancer patients showed no difference in rates of mortality, suspected DVT, PE, or bleeding events.[238]

For prevention of catheter-related VTE, randomized controlled studies have not established the efficacy of prophylactic doses of LMWH or low-dose warfarin (1 mg daily).[239-241] A recent randomized trial (n=944) showed that dose-adjusted warfarin of INR 1.5 to 2.0 was significantly more effective than fixed-dose warfarin of 1 mg daily in prevention of catheter-related VTE at a cost of a trend toward more bleeding. However, a separate comparison of warfarin between fixed 1 mg dose and adjusted dose of INR1.5 to 2 with placebo did not demonstrate a statistically significant reduction in VTE.[242] These data suggest that therapeutic or near-therapeutic doses of anticoagulation will likely be necessary for successful prevention of catheter-related VTE. Until additional data are available, the panel does not recommend VTE prophylaxis for cancer patients with a CVAD.

Outpatient Prophylactic Therapy in Ambulatory Cancer Patients

Certain groups of cancer patients are known to remain at risk for VTE after discharge from the hospital. In a retrospective observational study based on data from a large cohort of cancer patients (n=17,874) identified in a health care claims database, VTE (DVT or PE) occurred in nearly 6% of patients during the 12-month index period.[243] A significantly higher proportion of VTE events was diagnosed in the outpatient setting compared with the inpatient setting (78% vs. 22%; $P < .0001$). Moreover, among patients who had a VTE in the outpatient setting, 21% had been hospitalized within 30 days of the VTE event.[243] This observational study suggests that a high proportion of VTE occurs in the cancer outpatient setting, and underscores the need to better identify patients who may benefit from outpatient thromboprophylaxis. The risk for VTE is sufficiently high in some surgical and medical oncology patients that VTE prophylaxis should be considered in the outpatient setting. Cancer patients undergoing abdominal or pelvic surgery should be considered for outpatient prophylaxis.[244] Features that identify surgical oncology patients at higher risk for VTE include a previous episode of VTE, anesthesia times longer than 2 hours, advanced-stage disease, perioperative bed rest of 4 days or more, and patient aged 60 years or older.[15] Extended prophylaxis out to 4 weeks post-surgery was associated with a more than 50% reduction in venographic VTE in patients undergoing major abdominal surgery.[245,246] Since thromboembolic postoperative complications greatly exceeded hemorrhagic complications as a cause of death in the @RISTOS observational cohort study of cancer surgery patients,[15] extended VTE prophylaxis of up to 4 weeks is recommended for cancer surgery patients, particularly the high-risk patients undergoing abdominal or pelvic surgery.

Although there is a lack of consistent evidence to support extended outpatient prophylaxis in most populations of ambulatory medical oncology patients,[247] it is recommended for multiple myeloma patients receiving highly thrombogenic regimens. Immunomodulating agents with antiangiogenic properties, such as thalidomide or lenalidomide, have been associated with an increased incidence of VTE in patients with multiple myeloma in the absence of prophylaxis, although the reported rates of VTE vary widely across studies.[46,65,66,69,247,248] It appears that a number of factors contribute to thrombosis associated with thalidomide or its derivatives,[248] and VTE rates are especially high when thalidomide or lenalidomide is combined with high-dose dexamethasone of 480 mg per month, or doxorubicin or multi-agent chemotherapy regimens.[46,65,68-70] In a retrospective case-control study of thalidomide or lenalidomide combined with dexamethasone in newly diagnosed patients with multiple myeloma (n=411), the incidence of VTE among the subgroup of patients who received the combination with high-dose dexamethasone (480 mg per 28-day cycle) was 19% with thalidomide and 11% with lenalidomide.[249] Data regarding the use of routine thromboprophylaxis were not provided. In an open-label, randomized, non-inferiority trial comparing lenalidomide combined with high-dose dexamethasone (480 mg per 28-day cycle) versus with low-dose dexamethasone (160 mg per 28-day cycle) in previously untreated patients with multiple myeloma (n=445), the incidence of DVT was significantly higher among the patients receiving the combination with high-dose dexamethasone (26% vs. 12%; $P = .0003$).[250] Mandatory thromboprophylaxis was added to the study protocol after enrollment of approximately 60% of the patients. The package inserts for thalidomide and lenalidomide include “black box” warnings regarding the VTE risks associated with the administration of these agents.[251,252]

For patients with multiple myeloma, the panel recommends a prophylaxis strategy based on a risk-assessment model published by the International Myeloma Working Group.[46] In their publication, VTE prophylaxis with either LMWH (eg, enoxaparin 40 mg daily) or dose-adjusted warfarin (INR 2–3) is recommended for patients with multiple myeloma who are receiving lenalidomide- or thalidomide-based combination regimens associated with a high thrombotic risk or in patients with two or more

individual or disease-related risk factors (see Guidelines section on *VTE Risk Factors in Cancer Patients*, VTE-A 2 of 3). Aspirin prophylaxis (81–325 mg daily) is an option for multiple myeloma patients receiving thalidomide or lenalidomide with one or fewer individual or multiple myeloma-specific risk factors.[46]

In a recent phase III, open-label, multicenter, randomized trial in patients with previously untreated multiple myeloma (n=667) receiving thalidomide-containing regimens, both aspirin (100 mg daily) and fixed-dose warfarin (1.25 mg daily; dose adjustment allowed to maintain INR <3) were similarly effective in reducing thromboembolic events compared with LMWH (enoxaparin 40 mg daily).[253] The primary endpoint was a composite measure including symptomatic DVT, PE, arterial thrombosis, acute cardiovascular events, or sudden otherwise unexplained death during the first 6 months from randomization. The incidence of the composite endpoint was 6.4%, 8.2%, and 5% in the aspirin, warfarin, and LMWH groups, respectively.[253] The absolute risk for the composite endpoint was not statistically different when comparing aspirin with LMWH (absolute difference +1.3%; *P* = .544) or when comparing warfarin with LMWH (absolute difference +3.2%; *P* = .183). Although not statistically significant, LMWH was associated with trends for decreased risks for grade 3 to 4 thromboembolic events and major bleeding events when compared with aspirin. However, LMWH was associated with a significantly decreased risk for grade 3 to 4 thromboembolic events when compared with warfarin (absolute difference +5% for warfarin vs LMWH; *P* = .024). Moreover, among the subgroup of patients aged 65 years or older receiving combination therapy with bortezomib, melphalan, prednisone, and thalidomide, LMWH significantly reduced the risk for the composite endpoint compared with warfarin (absolute difference +11.3 for warfarin vs. LMWH; *P* = .006).[253] It should be noted that this study was conducted in myeloma patients with ”standard risk” for thromboembolism, who had no clinical indication for anticoagulation or antiplatelet therapy.

As part of a substudy of a phase III, open-label, randomized trial, thromboprophylaxis with aspirin (100 mg daily) was compared with LMWH (enoxaparin 40 mg daily) in patients with multiple myeloma (n=342) receiving lenalidomide-containing induction (combined with low-dose dexamethasone) and consolidation (combined with melphalan and prednisone).[254] The primary endpoint was a composite measure including symptomatic DVT or PE, arterial thrombosis, acute cardiovascular events, or otherwise unexplained sudden death during the first 6 months after randomization. The incidence of the composite endpoint was not statistically different, with 2.3% in the aspirin arm and 1.2% in the LMWH arm. The incidence of DVT was 1.1% and 1.2%, respectively, and the incidence of PE was 1.7% and 0%, respectively. No patients in either treatment arm experienced arterial thrombosis, acute cardiovascular events, or sudden deaths.[254] No major bleeding events occurred in either treatment arm; minor bleeding (involving the GI) was reported in 1 patient (<1%) in the LMWH arm. As in the case with the aforementioned phase III study of thromboprophylaxis in patients treated with thalidomide-containing regimens, the current study only included patients who had standard risk for VTE, who had no clear indication or contraindications for antiplatelet or anticoagulation therapy.[254] Nevertheless, LMWH appeared to be more effective in preventing PE in this patient population. The investigators from this trial suggested that LMWH was preferred for thromboprophylaxis in patients at high risk for VTE during induction therapy with lenalidomide-containing regimens; in patients with no or only 1 risk factor for VTE, aspirin may be an alternative option. In addition, the investigators concluded that aspirin may also be a feasible thromboprophylaxis option during consolidation or maintenance therapy with lenalidomide.[254]

In light of the published data from the phase III randomized trials above, the NCCN Panel recommends prophylactic aspirin in multiple myeloma

patients receiving thalidomide or lenalidomide (excluding high-risk combinations) who have no other risk factors for VTE.

With respect to other ambulatory cancer patients, the NCCN Panel suggests risks/benefits conversations regarding the option of thromboprophylaxis in individuals considered to be at high risk for VTE based on an assessment of VTE risk factors (see Guidelines section on *VTE Risk Factors in Cancer Patients*, VTE-A). Some cancer patients undergoing chemotherapy are at increased risk of developing VTE. A predictive model for chemotherapy-associated VTE has been developed[26] and independently validated in several studies. The Khorana model considers the following parameters to determine the overall risk for VTE in patients with cancer: site of primary cancer ("very high risk" for stomach or pancreatic cancer; "high risk" for lymphoma, lung, gynecologic, bladder, or testicular cancer), increased pre-chemotherapy platelet count (≥350 × 10^9/L), decreased hemoglobin level (<10 g/dL) or use of ESAs, increased pre-chemotherapy leukocyte count (>11 × 10^9/L), and high BMI (≥35 kg/m^2).[26] Using a scoring system that assigns risk points to each of the above parameters, patients with 0 points (none of the above risk parameters) are categorized as low risk, those with a total of 1 or 2 points are categorized as intermediate risk, and those with a total score of 3 or higher are considered high risk of developing VTE (see Guidelines section on *VTE Risk Factors in Cancer Patients*, VTE-A 3 of 3). In the original Khorana et al 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.[26] Subsequent independent studies evaluated the utility of the Khorana scoring system in patients with cancer. Retrospective studies in patients with solid tumors and malignant lymphomas reported symptomatic VTE rates of 5% in low-risk, 16% in intermediate-risk, and 27% to 41% in high-risk patient categories.[255,256] In a more recent prospective study in patients with cancer (n=819), the rates of symptomatic VTE based on the Khorana scores were 3.8% for low-risk, 9.6% for intermediate-risk, and 17.7% for high-risk patient groups.[50]

Data from a randomized, placebo-controlled, double-blind trial of patients with advanced cancer undergoing treatment with chemotherapy (PROTECHT trial) showed a statistically significant decrease in thromboembolic events (composite endpoint of venous and arterial) in the group receiving prophylactic LMWH (ie, nadroparin) compared with the placebo arm.[257] Further, in the randomized CONKO-004 trial, the symptomatic VTE rate of pancreatic cancer patients receiving chemotherapy was significantly reduced at 3 and 12 months with enoxaparin thromboprophylaxis (1mg/kg daily for 3 months followed by 40 mg daily for 3 months) compared with no LMWH.[258] Most recently, in a large phase III, randomized, placebo-controlled trial (SAVE-ONCO) in patients with advanced cancer receiving chemotherapy (n=3212), thromboprophylaxis with the investigational ultra-LMWH semuloparin 20 mg daily was compared with placebo.[259] The primary efficacy endpoint of this study was a composite endpoint comprising symptomatic DVT, nonfatal or fatal PE, and other death related to VTE. The main safety endpoint was clinically relevant bleeding events. The most common primary cancer sites were lung (37%) and colorectal (29%). Thromboprophylaxis was associated with a significant decrease in the primary endpoint compared with placebo (1.2% vs. 3.4%; hazard ratio, 0.36; 95% CI, 0.21–0.60; $P < .001$).[259] The benefit of thromboprophylaxis was observed for both symptomatic DVT (0.7% vs. 2.1%; hazard ratio, 0.32) and nonfatal or fatal PE (0.6% vs. 1.5%; hazard ratio, 0.41). Clinically relevant bleeding (2.8% vs. 2%) and major bleeding events (1.2% vs. 1.1%) with semuloparin versus placebo were not different. Survival outcomes were not significantly different between study arms, with deaths occurring in 43% and 44.5% of patients in the semuloparin and placebo arms, respectively.[259] It should be noted that semuloparin is

an investigational agent and has not been approved by the FDA for any indication.

Patients with cancer at high risk for VTE (based on Khorana risk assessment score 3 or higher[26]) could be considered for outpatient VTE prophylaxis on an individual basis. For these patients, the NCCN Guidelines Panel recommends discussions with patients/caregivers regarding the potential risks and benefits of administering VTE prophylaxis in the outpatient setting. However, thromboprophylaxis in the majority of cancer outpatients receiving chemotherapy is controversial and its broader application using the Khorana risk assessment model or the Vienna risk assessment model should await the results of randomized controlled trials evaluating the efficacy of risk-adjusted thromboprophylaxis based on these models.[260]

Mechanical Prophylaxis

Intermittent pneumatic compression (IPC) devices and GCS are mechanical prophylaxis options that are principally used in patients with contraindications to pharmacologic prophylaxis or in conjunction with pharmacologic agents in patients at very high risk for VTE. Mechanical prophylaxis should not be used in patients with an acute DVT or in the setting of severe atrial insufficiency (the latter pertains to GCS). In addition, consideration of risks and benefits should be weighed in the presence of large hematomas, thrombocytopenia (platelet count <20,000/mcL), skin ulceration or wounds (which may be more of a concern with GCS), mild arterial insufficiency (which pertains to GCS only), or peripheral neuropathy (which pertains to GCS only; see Guidelines section on *Contraindications to Mechanical Prophylaxis*, VTE-B). Whenever mechanical prophylaxis is employed, steps should be taken to ensure its proper use and continuous application.

IPC devices have been less well-studied than the use of anticoagulation therapy in VTE prevention.[182] Most of the data on the effectiveness of mechanical prophylaxis have come from surgical populations. For example, in a study comparing the VTE rate in gynecologic oncology surgery patients receiving either low-dose heparin 3 times a day (starting with the day before surgery and continuing for 7 days or longer after surgery) or IPC of the calf, no difference was seen between the 2 modalities.[261] A retrospective evaluation of high-risk colorectal surgery patients who had received mechanical prophylaxis without anticoagulant therapy indicated that IPC devices were effective in preventing postoperative VTE.[262] However, results from a retrospective study of 839 patients over a 2-year period who had undergone abdominal surgery for gynecologic cancers and received pneumatic compression and early ambulation for VTE prophylaxis found that the incidence of PE in cancer patients (4.1%) exceeded by 14-fold the incidence of PE in patients with benign disease (0.3%).[244] Therefore, IPC devices should only be used alone for VTE prophylaxis in patients for whom anticoagulant prophylaxis is contraindicated.

GCS have been demonstrated to significantly reduce VTE in comparison to no prophylaxis and provide even greater protection when combined with other preventive therapies.[263] However, many of these studies were conducted more than a decade ago and used fibrinogen uptake scans as a primary outcome measure—a now antiquated diagnostic method. In addition, very few of the patients were noted to have malignancies. Furthermore, a randomized controlled trial in patients undergoing hip surgery found that GCS did not provide significant additive protection against VTE in patients receiving fondaparinux 2.5 mg daily for 5 to 9 days, suggesting that GCS may not have significant clinical benefits in patients able to receive more potent forms of VTE prophylaxis.[264] Similarly, recent results from the CLOTS1 trial, which randomly assigned patients within 1 week of stroke to routine care with or without GCS, found that

GCS did not reduce the incidence of DVT in these patients and was associated with a 4-fold increase in the frequency of skin ulcers and necrosis.[265] However, the patient group studied in the CLOTS1 trial differs considerably from the patient population described in these guidelines. Furthermore, the long delay in the institution of prophylaxis and the prolonged duration of GCS use (up to 30 days in over 70%) indicate that the safety and efficacy of GCS may be different in different populations studied under different conditions. Therefore, further investigation is warranted.

Until data become available, GCS should not be relied on as the sole method of VTE prophylaxis in cancer patients. Furthermore, cancer patients prescribed GCS for VTE prophylaxis should be carefully monitored for skin complications.

VTE Treatment

Upon diagnosis of VTE, the panel recommends beginning immediate treatment with weight-based intravenous UFH, LMWH, or, in some cases, fondaparinux in cancer patients without contraindications to anticoagulation. Treatment should be at least 5 to 7 days in duration. Since chronic therapy with LMWH is associated with superior outcomes in cancer patients with VTE, its use in the acute phase of treatment may be preferable unless contraindications exist. In the event that warfarin will be used for chronic therapy, there should be a short-term transition phase of at least 5 days during which the acute parenteral anticoagulant (UFH, LMWH, or fondaparinux) is overlapped with warfarin until an INR of 2 or more is achieved. Cancer patients with a DVT or PE should be treated for a minimum duration of 3 months with either an LMWH or warfarin.[183,266] LMWH as monotherapy without warfarin is recommended for the first 6 months of chronic treatment of proximal DVT or PE, and for prevention of recurrent VTE in patients with advanced or metastatic cancer who do not have contraindications to anticoagulation (category 1). However, issues such as patient preference and cost should also be considered. Anticoagulation for an indefinite duration should be considered in patients with active cancer or persistent risk factors. Since the chronic treatment of VTE with LMWHs has not been evaluated in clinical trials of cancer patients for durations longer than 6 months, decisions to continue LMWH beyond this time frame or to switch to warfarin therapy for patients requiring longer durations of anticoagulation therapy should be based on clinical judgment.

IVC filter placement should be strongly considered for patients with acute proximal lower-extremity DVT or PE who have absolute contraindications to anticoagulation.[183,266] However, the benefit of placing an IVC filter in the absence of a lower-extremity IVC or pelvic DVT is unclear. An IVC filter should also be considered in patients with PE where anticoagulation was ineffective (category 2B), patients who are non-adherent with prescribed anticoagulation (category 2B), those with baseline cardiac or pulmonary dysfunction severe enough to make any new or recurrent PE life-threatening (category 2B), and those with documented multiple PE and chronic thromboembolic pulmonary hypertension (category 2B).

In general, a retrievable IVC filter is preferred in most clinical situations; permanent filters should only be considered in rare situations in which patients have permanent contraindications to anticoagulation or chronic comorbidities that preclude the use of anticoagulants. When a retrievable filter is placed, it is imperative that patients be followed closely by their physicians so that the device can be removed in a timely fashion after the need for its placement is no longer present.

Improvements in technology and an increase in the number of available thrombolytic agents have increased the use of thrombolytic therapy for DVT. Anticoagulation prevents clot extension and recurrence, but does not actively dissolve clot. In contrast, thrombolytic agents promote clot dissolution, which may help to limit long-term complications such as post-

thrombotic syndrome (PTS). PTS is a chronic complication of DVT that develops over months to years after the thrombotic episode. PTS is caused by chronic venous hypertension that results from impaired venous outflow from the affected limb due to vascular obstruction and venous valvular dysfunction. Thrombolytic agents theoretically may reduce the incidence of PTS by promoting rapid clot lysis, reducing venous outflow obstruction, and preventing venous valvular damage. Typical symptoms and signs of PTS include leg pain, heaviness, or swelling of the leg.[267] The syndrome has been reported to occur in approximately 30% to 50% of patients within 5 to 8 years following symptomatic DVT, and can negatively affect a patient's quality of life.[268,269] Severe forms of PTS can occur in up to 10% of patients, and may involve skin and subcutaneous tissue changes, such as skin ulcerations, hyperpigmentation, varicose eczema, and subcutaneous atrophy.[267]

Thrombolytics that have been used in the management of DVT include urokinase, streptokinase, and, more recently, recombinant plasminogen activators alteplase, reteplase, and tenecteplase given intravenously. In the past, thrombolytic agents were delivered systemically through an intravenous catheter, which likely reduced the efficacy of the therapy and increased the likelihood of bleeding complications. Nevertheless, thrombolysis was associated with increased rates of major or complete clot lysis and fewer post-thrombotic complications, compared with anticoagulation alone.[270-275] In recent years, catheter-directed delivery of thrombolytic agents directly into the substance of the clot has allowed more localized targeting of thrombolytic agents and the employment of catheter-based thrombectomy devices to accelerate clot removal. Catheter-directed thrombolysis (CDT) with or without mechanical thrombectomy is associated with significantly higher rates of complete clot lysis than conventional anticoagulation.[276] Effective clot lysis in patients with DVT has been reported with CDT using urokinase, alteplase, reteplase, and tenecteplase,[277-279] including a retrospective analysis that suggested potentially lower treatment costs associated with plasminogen activators (alteplase and reteplase) compared with urokinase.[278]

Initial results from an open-label, randomized, controlled trial comparing CDT with alteplase added to anticoagulation versus anticoagulation alone in patients with acute iliofemoral DVT (n=103) reported a higher rate of iliofemoral patency at 6 months with the addition of CDT (64% vs. 36%).[280] Long-term follow-up from this study with larger patient numbers (n=209) confirmed the higher rate of iliofemoral patency at 6 months (66% vs.47%) with the addition of CDT.[281] After completion of 24 months of follow-up, PTS was reported in significantly fewer patients in the CDT arm (41% vs. 56%; P = .047). In contrast, ECS did not prevent PTS compared to placebo in a randomized trial (SOX Trial) of patients who experienced a first proximal DVT.[282] Therefore, GCS should not be prescribed for prevention of PTS.

Retrospective patient series have demonstrated that cancer patients can benefit from catheter-directed pharmacomechanical thrombolysis.[283] The 2012 ACCP 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 less than 14 days; good functional status; life expectancy of at least 1 year; and low risk of bleeding.[183] The NCCN Panel believes that CDT and thrombectomy can be considered a therapeutic option for select patients with large symptomatic extremity DVT, particularly when they are not responding to conventional anticoagulation.[266] Absolute contraindications to thrombolysis (administered locally or systemically) include history of hemorrhagic stroke (or stroke of unknown origin), intracranial tumor, ischemic stroke (in previous 3 months), history of major trauma, surgery or head injury in previous 3 weeks, low platelet count (<100 × 10^9/L), active bleeding, and bleeding diathesis. Relative contraindications to thrombolysis include age greater than 75 years, pregnancy or first

postpartum week, non-compressible puncture sites, traumatic resuscitation, refractory hypertension, advanced liver disease, infective endocarditis, recent GI bleeding within 3 months, and life expectancy of 1 year or less.[183] Selection of thrombolytic agents and thrombectomy devices should be made based on local expertise and experience. Broader use of CDT awaits the outcome of currently active clinical trials.

Treatment of patients with an incidental VTE following radiographic detection should be the same as for patients with symptomatic VTE.[135,284,285]

Immediate VTE Treatment

In a recent meta-analysis of trials comparing outcomes with anticoagulants (UFH, LMWH, and fondaparinux) as initial treatment of VTE in cancer patients, LMWH was associated with a significant reduction in mortality rate at 3-month follow-up compared with UFH (relative risk, 0.71; 95% CI, 0.52–0.98).[286] However, no significant difference was found in VTE recurrence between LMWH and UFH. No statistically significant differences were found between heparin and fondaparinux in terms of mortality, VTE recurrence, or bleeding events.[286] In the absence of contraindications to their use, LMWHs are preferred for acute management of VTE in cancer patients because they do not require hospitalization or monitoring, and are the preferred option for long term therapy.

Chronic VTE Treatment

Several studies comparing the efficacy and safety of LMWH and oral warfarin in the chronic treatment of VTE in patients with cancer have been performed. In a randomized open-label trial (CANTHANOX trial), the use of chronic (3 months) enoxaparin (1.5 mg/kg every 24 hours) versus chronic warfarin (INR 2–3) was evaluated after immediate treatment with either LMWH or UFH in 146 cancer patients with VTE.[169] The primary endpoint of this study was a combined outcome event including major bleeding and recurrent VTE within 3 months. In the groups receiving chronic enoxaparin and warfarin, 10.5% and 21.1% of patients, respectively, experienced either major bleeding or recurrent VTE (P = .09); fatal bleeding occurred in 0% and 8% of patients, respectively (P = .03). In another study, no significant differences in bleeding or recurrent VTE were observed when patients with active cancer and acute VTE were randomly assigned to receive either 6 months of enoxaparin (either 1.5 mg/kg or 1 mg/kg every 24 hours) or immediate enoxaparin therapy followed by warfarin to complete 6 months of therapy (ONCENOX trial).[287]

The CLOT trial compared the efficacy and safety of immediate dalteparin (200 units/kg daily for 5–7 days) followed by chronic (6 months) therapy with an oral coumarin derivative versus chronic dalteparin therapy (200 units/kg daily for one month followed by 150 units/kg for months 2–6) in patients with cancer (most had metastatic disease) after diagnosis of acute proximal DVT, PE, or both.[168] The Kaplan-Meier estimate for recurrence of VTE over the 6-month study period showed significantly decreased risks with dalteparin compared with oral anticoagulants (hazard ratio, 0.48; P = .002). This study showed probabilities of recurrent VTE at 6 months of 9% and 17% in cancer patients receiving dalteparin or oral anticoagulants, respectively. No significant difference in bleeding rates was seen for the 2 groups.[168] The results of this study support use of LMWHs as chronic anticoagulation therapy in patients with metastatic disease who are diagnosed with acute VTE.

Some limitations of the CLOT study include the lack of patients with below-the-knee or catheter-related thrombosis; a study duration of only 6 months, for which the apparent efficacy difference was observed for development of recurrent DVT only (but not for PE, although the study was not designed to assess differences in outcomes according to type of VTE); and uncertainty as to whether these results can be extrapolated to

LMWHs other than dalteparin. A Cochrane review of anticoagulation for the chronic treatment of VTE in patients with cancer combined the results of all these studies and found no significant differences in bleeding, thrombocytopenia, or survival outcomes with use of LMWH compared with oral vitamin K antagonists.[288] However, the incidence of VTE was significantly lower for patients receiving LMWH (hazard ratio, 0.47; 95% CI, 0.32–0.71).

In a recent open-label, randomized, phase III trial in patients with acute PE with or without DVT (n=4832), treatment with the oral factor Xa inhibitor rivaroxaban (15 mg twice daily for the first 3 weeks, then 20 mg once daily thereafter) was compared with standard therapy with LMWH and vitamin K antagonist (enoxaparin 1 mg/kg twice daily for at least 5 days, and vitamin K antagonist adjusted to INR 2.0–3.0) for initial and chronic treatment (3, 6, or 12 months).[206] This study was designed as a non-inferiority trial. The primary efficacy endpoint was symptomatic recurrent VTE, defined as a composite endpoint comprising fatal or nonfatal PE or DVT. The main safety endpoint was clinically relevant bleeding. Based on the primary endpoint of recurrent VTE, rivaroxaban was found to be non-inferior to standard therapy (2.1% vs. 1.8%; hazard ratio, 1.12; 95% CI, 0.75–1.68).[206] The incidence of clinically relevant bleeding events was not significantly different between rivaroxaban and standard therapy (10.3% vs. 11.4%; hazard ratio, 0.90; 95% CI, 0.76–1.07). However, rivaroxaban was associated with a significantly decreased incidence of major bleeding (1.1% vs. 2.2%; hazard ratio, 0.49; 95% CI, 0.31–0.79; $P = .003$).[206] This randomized study suggested that initial and chronic treatment of PE with fixed-dose rivaroxaban was non-inferior to standard anticoagulation therapy. It should be noted that less than 5% of the study patients in this study had active cancer.

Apixaban is another oral factor Xa inhibitor that has also been evaluated for extended anticoagulation therapy in patients who had a VTE. In a recent double-blind, randomized, phase III trial in patients who had completed 6 to 12 months of anticoagulation for VTE (n=2486), extended treatment with apixaban (at a dose of 2.5 mg or 5 mg twice daily) was compared with placebo given for 12 months.[213] The primary outcome measure was a composite endpoint comprising symptomatic recurrent VTE (fatal or nonfatal PE or DVT) and death from any cause. During the 12-month treatment period, the primary endpoint occurred in 3.8% of patients in the 2.5 mg apixaban arm and 4.2% in 5 mg apixaban arm compared with 11.6% in the placebo arm ($P < .001$ for both comparisons). The rate of symptomatic recurrent VTE and death from VTE was also significantly reduced with apixaban 2.5 mg (1.7%) or apixaban 5 mg (1.7%) compared with placebo (8.8%; $P < .001$ for both comparisons).[213] The rate of major bleeding was 0.2% in the 2.5 mg apixaban arm, 0.1% in the 5 mg apixaban arm, and 0.5% in the placebo arm. This study showed that extended anticoagulation with apixaban reduced the risk for recurrent VTE without increasing the risk for major bleeding. It should be noted, however, that less than 2% of patients on this study had active cancer.[213] Thus, the use of apixaban for acute and extended chronic treatment of VTE in patients with cancer remains to be investigated in future prospective trials.

Increased survival rates have been reported for subgroups of cancer patients receiving chronic treatment with LMWH versus other VTE therapies or placebo.[289,290] For example, although no survival differences were seen in groups of patients with advanced cancer without VTE receiving either dalteparin or placebo in the FAMOUS study, results from a subgroup analysis of patients with better prognoses (more indolent disease and survival beyond 17 months post-randomization) suggested that 2- and 3-year survival rates were higher for patients receiving dalteparin compared with patients receiving placebo.[200] A post hoc analysis of patients from the CLOT study also indicated that no differences in 1-year survival were seen between groups of patients with metastatic

disease receiving either long-term dalteparin or oral coumarin derivatives, whereas 1-year survival rates were higher in the subgroup of patients without metastases receiving dalteparin when compared with patients in the same subgroup receiving an oral vitamin K antagonist.[290] Results of other randomized studies have also provided evidence of improvement in median progression-free survival and/or overall survival of cancer patients receiving LMWHs.[291,292] In addition, a Cochrane review assessing the antineoplastic properties of anticoagulants found that heparins appear to improve the survival of cancer patients with limited-stage disease and that further research is warranted to identify the most effective regimens and most responsive cancer patient populations.[293] Additional evaluations of the putative anti-tumor effects of LMWHs are needed before recommendations pertaining to their use as antineoplastic agents can be made.

Treatment of Catheter-related DVT

The central tenant guiding the treatment of catheter-related DVT is based on the question of whether the device is required for continued treatment of the patient. Device removal is recommended in the case of catheter-related DVT when the device is no longer required, or when it is required but contraindications to anticoagulation exist. If device removal is planned, some have recommended a short period of anticoagulation of 5 to 7 days, if feasible, to reduce the chances of clot embolization with device removal. An assessment of the likelihood and consequences of clot embolization based on the size and position of the device-associated thrombus should be conducted prior to removal. Anticoagulation therapy is recommended while the catheter is in place (in the absence of contraindications) and for a total duration of therapy of at least 3 months, or for as long as the catheter remains in place, whichever is longer. Consider removal of the catheter if DVT symptoms persist or if the catheter is infected, dysfunctional, or no longer necessary. Patients with catheter-related DVT and contraindications to anticoagulation therapy should be followed for changes in these contraindications as clinically indicated; anticoagulation therapy is recommended after contraindications are no longer present.

No randomized controlled trials have been reported evaluating the effects of particular therapeutic strategies on outcomes of catheter-related VTE. A prospective study of 444 cancer patients with CVAD showed an incidence of symptomatic catheter-related thrombosis of 4.3%.[75] Of 19 patients with catheter-related thrombosis, 9 were treated with anticoagulation therapy only, 8 patients underwent anticoagulation therapy and catheter removal, 1 patient was treated with catheter removal only, and 1 patient did not receive any treatment. The duration of anticoagulation therapy was not specified, but evaluation of the 15 patients alive at 24 weeks after diagnosis of catheter-related thrombosis revealed that residual symptoms were present in only 2 patients. A more recent pilot study of cancer patients with catheter-related, symptomatic UEDVT demonstrated that anticoagulation with dalteparin followed by warfarin (INR 2–3) was not associated with episodes of recurrent VTE and/or line removal as a consequence of thrombosis/infusion failure; major bleeding occurred in 3 patients (4%).[294]

Treatment of SVT

Anticoagulation therapy with intravenous UFH or a LMWH for at least 6 weeks is a category 2B recommendation for patients with a non-peripheral catheter-related SVT in close proximity to the deep venous system. Consider treating up to 12 weeks if SVT is in close proximity to the common femoral vein. Since migratory superficial thrombophlebitis is a characteristic presentation for Trousseau's syndrome, a heightened awareness of this cancer-associated hypercoagulable state is warranted as indefinite therapy with UFH or LMWH is essential for its treatment.

Catheter removal is recommended for a peripheral catheter-related SVT. Anti-inflammatory medications, warm compresses, and elevation of the

affected limb should be employed as clinically indicated. These strategies are also recommended for the initial treatment of SVT that is not associated with a peripheral catheter. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients with platelet counts less than 20,000 to 50,000/mcL or with severe platelet dysfunction. Anti-inflammatory agents are recommended for the symptomatic treatment of certain types of SVT only, not for DVT prophylaxis. Only a limited number of studies have evaluated the clinical significance of SVT, its associated progression to VTE, and the effect of anticoagulant agents on its course.[295,296] In a large observational study of patients (n=844) with symptomatic SVT (at least 5 cm), 66% had SVT of the greater saphenous vein, and in 20% of these patients the median distance between the thrombus and the saphenofemoral junction was less than or equal to 3 cm.[96] In this study, 25% of patients had DVT or PE at inclusion, and 10% of the patients without VTE at study inclusion (isolated SVT only) who were available at 3-month follow-up subsequently developed thromboembolic complications (eg, PE, DVT, extension of SVT) despite the use of anticoagulation therapy in about 90% of these individuals[96]; a possible limitation of this study is that all of these patients were evaluated in a specialist referral setting. In a prospective assessment of 60 consecutive patients with SVT of the greater saphenous vein, the combined incidence of DVT and SVT events over a 6-month follow-up period was lower in patients treated with twice-daily subcutaneous injections of high-dose heparin (12,500 IU for 1 week, followed by 10,000 IU for 4 weeks) when compared with patients receiving 4 weeks of low-dose (5000 IU) heparin (3% vs. 20%; $P = .05$).[297] A pilot study evaluating the effects of once-daily administration of an LMWH, an NSAID, or placebo for 8 to 12 days on the clinical course of SVT showed no significant differences between treatment and placebo groups with respect to progression to DVT.[298] However, all active treatments reduced the combined rate of DVT and SVT compared with placebo, although no significant differences were observed between active treatment groups.[298] This finding possibly indicates that longer treatment durations may be required.

In a placebo-controlled, randomized, double-blind study (CALISTO), Decousus and colleagues randomized 3002 patients with acute symptomatic superficial thrombophlebitis of the lower extremities to fondaparinux 2.5 mg daily (n=1502) or placebo (n=1500) for 45 days. Fondaparinux was associated with a significant reduction in the primary outcome (all-cause mortality, symptomatic VTE, or extension of the superficial thrombophlebitis to involve the saphenofemoral junction or symptomatic recurrence of SVT) compared with placebo (0.9% vs. 5.9%; relative risk reduction [RRR], 85%; 95% CI, 0.74–0.92; $P < .0001$).[299] Fondaparinux 2.5 mg daily significantly reduced the incidence of DVT and/or PE (0.2% vs. 1.3%; RRR, 85%; 95% CI, 0.50–0.95; $P < .001$). The rate of major bleeding was similar (1 patient in each group). The trial establishes the efficacy of prophylactic dose fondaparinux in the treatment of SVT. However, it is important to note that patients with active cancer and SVT within 3 cm of the saphenofemoral junction were excluded.[299]

Treatment of SPVT

The management of patients with SPVT encompasses the use of anticoagulation therapy with or without invasive procedures, such as CDT, (TIPS), surgical shunting, or surgical resection of bowel, as well as other medical management, such as the use of a β-blocker. Management depends on the extent and location of the thrombus, presence of acute symptoms of intestinal infarction, and signs of portal cavernoma or portal hypertension. In the absence of contraindications, anticoagulation with unfractionated heparin or LMWH (preferred) should be initiated, followed by oral anticoagulation for at least 6 months in the case of triggered thrombotic events, such as in a postsurgical setting.[106,108,114,115] The benefit of anticoagulation as initial and long-term therapy in patients with SPVT has been reported in several studies.[102,117,300,301] In a long-term follow-up

study of patients with SPVT (n=95; median follow-up of 41 months) primarily treated with anticoagulation (LMWH 200 IU/kg per day for 7–10 days followed by oral anticoagulation for 6 months), 45% of patients with acute SPVT (n=21) had complete recanalization with anticoagulants.[102] Patients requiring resection for intestinal infarction or having 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 was significantly more frequent among patients with concurrent myeloproliferative disorders at presentation versus those without such disorders (70% vs. 13%; $P < .0001$). Moreover, recurrent VTE was only observed among patients who did not receive anticoagulation.[102] Gastrointestinal (GI) bleeding occurred in 15% of patients and was significantly more frequent among patients with bleeding from esophageal varices at presentation compared with those without prior bleeding (57% vs. 5%; $P < .0001$). None of the patients receiving oral anticoagulation had bleeding events.[102] In a recent prospective multicenter study in patients with acute portal vein thrombosis (n=95) treated with anticoagulation (initial therapy with heparin followed by oral anticoagulation targeting INR 2–3 for 6 months or long-term in patients with permanent prothrombotic disorders or obstruction of mesenteric vein), the 1-year recanalization rate in the portal vein was 38%.[117] The 1-year recanalization rates in the mesenteric and splenic veins were 61% and 54%, respectively. GI bleeding occurred in 9% of patients, none of which were fatal events.[117] Anticoagulation appears to lower the risk for recurrent thrombosis in patients with SPVT without increasing the risks for severe bleeding,[102,117,300,301] including in patients with underlying prothrombotic states.[300] However, a recent retrospective study in a large cohort of patients with SPVT (n=832) showed that the rate of recurrent VTE was not significantly improved with oral anticoagulation with warfarin (10-year recurrence-free survival rate was 89% vs. 77% in patients who did not receive anticoagulation; $P = .38$).[101] Based on multivariate analysis, hormone therapy was the only independent predictor of recurrence. Major bleeding events were reported more frequently among patients receiving anticoagulation compared with those who did not (26% vs. 19%; $P < .05$). Moreover, based on multivariate analysis, presence of gastroesophageal varices and anticoagulation were independent predictors for bleeding events.[101] In chronic SPVT, the presence of portal 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.[100] 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 patient's risk factor(s) for SPVT should be taken into consideration when weighing the risks and benefits of long-term anticoagulation. The panel currently recommends lifelong anticoagulation in patients with active cancer, underlying thrombophilia, and/or idiopathic thrombosis.

In patients with acute SPVT with clinical deterioration or progression of thrombosis despite anticoagulation, more invasive approaches using CDT, TIPS, or surgical shunting may be required.[106,108,115] 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.[102,104,108,114] Catheter-directed thrombolytic therapy has been reported to have some success in acute SPVT in small retrospective studies. [302-305] Thrombolytic therapy may be most suitable when administered locally for patients with recent thrombosis[115,304]; however, this approach should be used with caution due to risks for major bleeding complications.[114,115,302,305] The decision for administering thrombolytic therapy should be based on availability and expertise at the local institution, the location of the thrombus, and evaluation of risks of bleeding in individual patients. In addition, the selection of regimens should be based on institutional experience, with decisions made in conjunction with specialists in interventional radiology

and vascular surgery. For patients with acute hepatic vein thrombosis with contraindications to anticoagulation or for patients with chronic hepatin vein thrombosis for whom medical management alone are unsuccessful, TIPS or surgical shunts may be considered. TIPS is an interventional radiologic procedure that creates a portocaval shunt between the hepatic and portal veins, and may be appropriate for patients with an occluded IVC or a portacaval pressure gradient <10 mm Hg.[115,306] TIPS may also be appropriate for patients with refractory ascites and progressive hepatic dysfunction despite medical management and/or interventions to achieve recanalization.[306,307] 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.[306-311] 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% in recent studies.[306,311] Surgical portosystemic shunts may be appropriate in patients without an occluded IVC, with a portacaval pressure gradient >10 mm Hg, and with preservation of hepatic function.[115,312] The impact of surgical shunts versus other interventions on long-term outcomes is unknown[313]; nevertheless, 5-year survival rates range from 75% to 87% in patients with Budd-Chiari syndrome undergoing successful surgical portosystemic shunts,[314-316] and this procedure may improve survival outcomes in patients with intermediate-risk prognostic factors as defined by Darwish Murad et al.[317] Of note, surgical shunts appear to have largely been replaced with TIPS in recent years.[307]

Patients with chronic portal or mesenteric vein thrombosis frequently present with cavernous transformation and/or signs of portal hypertension, the latter of which can lead to complications such as variceal bleeding.[116] Gastroesophageal varices may be seen in 35% to 50% of patients with portal vein thrombosis at presentation,[101,114] and remain a significant independent risk factor for major bleeding in patients with SPVT.[101] Thus, an important goal in the management of patients with chronic portal or mesenteric thrombosis is risk reduction for and prevention of bleeding events.[108,114] The use of β-blockers and endoscopic treatments has been evaluated in the primary and secondary prophylaxis for variceal bleeding in patients at high risk of bleeding events. In several prospective randomized studies comparing the use of variceal banding ligation versus propranolol for primary prophylaxis of variceal bleeding in cirrhotic patients presenting with high-risk gastroesophageal varices, the treatment methods were similarly effective in preventing variceal bleeding (which occurred in 12%–25% of patients with ligation versus 24%–29% receiving propranolol), with a similar overall mortality rate.[318-320] In one of the studies, patients (n=75) treated with variceal banding ligation had a significantly decreased incidence of esophageal variceal bleeding compared with patients receiving propranolol (5% vs. 25%; *P* = .027), but at the expense of a higher incidence of subcardial variceal bleeding (8% vs. 0%; *P* = .027).[318] In another prospective randomized trial comparing the effectiveness of primary prophylaxis using these methods in cirrhotic patients (n=60), ligation was reported to be more effective than propranolol in preventing variceal bleeding (which occurred in 7% vs. 30%; *P* = .043).[321] A large randomized study comparing variceal banding ligation with or without propranolol for primary prophylaxis of variceal bleeding in patients with high-risk varices (n=144) showed that the combined modality did not significantly reduce the risks of bleeding (actuarial probability, 7% vs. 11%; *P* = .72) or death (actuarial probability, 8% vs. 15%; *P* = .37) at 20 months compared with ligation alone.[322] The use of variceal banding ligation and propranolol has also been evaluated in the secondary prophylaxis setting in patients with noncirrhotic portal hypertension at risk of recurrent variceal bleeding. In a recent study (n=101), the incidence of recurrent variceal bleeding was found to be similar between patients receiving ligation versus propranolol (24% vs. 18%; *P* = .625) for prevention of recurrent bleeding.[323] However, a recent meta-analysis of randomized studies demonstrated that variceal banding ligation or

sclerotherapy combined with β-blockers 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), suggesting that combined modality may be preferred as secondary prophylaxis for esophageal variceal bleeding.[324] The panel recommends initiation of β-blockers in patients with chronic portal or mesenteric thrombosis presenting with gastroesophageal varices with or without signs of portal hypertension. In patients who had prior variceal bleeding, it may be appropriate to consider variceal banding ligation or sclerotherapy in conjunction with β-blockers.

Treatment of PE

Once a diagnosis of PE is made, the panel recommends that patients be risk-stratified to determine the advisability of outpatient management and intensity of initial follow-up and treatment.[145,146] Anticoagulation therapy is recommended for all patients with acute PE who do not have a contraindication to such therapy.[183] In patients with a contraindication to anticoagulation, an IVC filter should be strongly considered if PE is due to lower extremity, pelvic, or abdominal DVT and the patient should be closely followed for a change in clinical status that would allow anticoagulation to be instituted.[183,266]

In patients with submassive PE and evidence of moderate or severe RV enlargement or dysfunction, thrombolytic therapy is a therapeutic consideration.[132,266,325] In patients without contraindications to anticoagulation, immediate anticoagulation therapy should be started at PE diagnosis; evaluation of risk should be performed concurrently with PE diagnosis or as soon as relevant data are available. After assessment of the cancer status of the high-risk patient with PE, the physician should consider the use of thrombolytic therapy and/or pulmonary embolectomy after weighing the severity of the patient's illness and his or her risk of bleeding. Although IVC filters are typically reserved for patients with a contraindication to anticoagulation, IVC filters are occasionally placed in patients with severely compromised cardiopulmonary status. In either case, a retrievable filter with a wide window of retrievability is preferred over a permanent one to allow subsequent filter retrieval once the patient's cardiopulmonary status has stabilized. Patients should be followed closely and their filters should be retrieved once they are stable on therapeutic anticoagulation. Permanent filters should only be considered for rare patients with chronic comorbidities or with permanent contraindication to anticoagulation.

In the randomized placebo-controlled MAPPET-3 trial of hemodynamically stable patients with submassive acute PE and pulmonary hypertension or evidence of RV dysfunction who received heparin in conjunction with thrombolysis with alteplase or heparin plus placebo, addition of thrombolysis was associated with significantly decreased incidence of in-hospital mortality and clinical deterioration requiring treatment escalation (primary endpoint; 11% vs. 25%; *P* = .006). 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.[326] The clinical endpoints and other aspects of the design of this trial have been criticized.[327,328] The recently published PEITHO study found similar results. The investigators randomized 1005 patients with intermediate risk submassive PE to tenecteplase plus heparin or placebo plus heparin. Death or hemodynamic decompensation occurred in 13 of 506 patients (2.6%) in the tenecteplase group as compared with 28 of 499 (5.6%) in the placebo group (odds ratio, 0.44; 95% confidence interval, 0.23 to 0.87; *P* = .02). There was no difference in death between the two groups (6 tenecteplase patients (1.2%) versus 9 placebo patients (1.8%)(*P* = .42). Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and 6 patients (1.2%) in the placebo group (P < .001). Stroke occurred in 12 patients (2.4%) in the tenecteplase group (hemorrhagic in

10) and 1 patient (0.2%) in the placebo group (P = .003). These data indicate that tenecteplase can reduce the incidence of hemodynamic decompensation in patients with intermediate risk PE but at the cost of increased extracranial bleeding and stroke and no improvement in mortality. Seventy-three patients (7.3%) on the PEITHO study had active cancer.

In a meta-analysis of 16 trials that randomized 2115 patients with PE to thrombolytic therapy or anticoagulation, use of thrombolytic therapy was associated with lower all-cause mortality (OR, 0.53; 95% CI, 0.32–0.88) and higher risk of major bleeding (OR, 2.73; 95% CI, 1.91–3.91).[329] This analysis included 8 trials involving patients with intermediate-risk PE (hemodynamically stable patients with right ventricular dysfunction). Results from previous 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.[330-334] Reports from several studies evaluating the use of pulmonary embolectomy in patients with acute PE provide support for the use of this procedure in patients with hemodynamically stable or unstable acute PE characterized by RV dysfunction.[335-337] An important consideration for these guidelines is that none of these studies evaluating the use of thrombolytic therapy or surgical embolectomy to treat patients with acute PE specifically address treating cancer patients. However, no significant difference in bleeding risk was observed in a recent retrospective consecutive case series comparing the safety of percutaneous CDT for upper- or lower-extremity acute symptomatic DVT in patients with or without cancer.[283]

The ACCP recommends against the use of thrombolytic therapy or pulmonary embolectomy in most patients with PE.[183] Use of thrombolytic therapy in selected patients, such as those with PE associated with hypotension or hemodynamic instability, and without a high risk of bleeding, is recommended.[183,266] Absolute contraindications to thrombolysis (administered locally or systemically) include a history of hemorrhagic stroke (or stroke of unknown origin), intracranial tumor, or ischemic stroke in previous 3 months, a history of major trauma, surgery or head injury in the previous 3 weeks, thrombocytopenia (platelet count $<100 \times 10^9$/L), active bleeding, and a bleeding diathesis. Relative contraindications to thrombolysis include older age (>75 years), pregnancy or first postpartum week, non-compressible puncture sites, traumatic resuscitation, refractory hypertension, advanced liver disease, infective endocarditis, recent GI bleeding in the last 3 months, and a life expectancy of 1 year or less.[183] Catheter or surgical embolectomy may be considered in patients with massive PE who have contraindications to thrombolytic therapy or those who remain unstable following thrombolysis.[183,266] Selection of thrombolytic agents and thrombectomy devices should be made based on local expertise and experience.

VTE Therapies: Response Assessment

Intensive monitoring of the antithrombotic effects of some anticoagulants is particularly important in patients with cancer.[192] The recommendations on monitoring anticoagulant response included in the NCCN Guidelines for VTE may be superseded by written standard procedures specific to an institution.

Unfractionated Heparin

Heparins indirectly affect the coagulation system by potentiating antithrombin activity, thereby facilitating inhibition of thrombin, factor Xa, and, to a lesser extent, several other activated coagulation factors.[181,338] The aPTT measures the overall activity of the intrinsic and common coagulation pathways and is particularly sensitive to agents that inhibit thrombin.[191,339] Therefore, UFH is most commonly monitored during the treatment of VTE with the aPTT and depends on the establishment of a therapeutic aPTT range.[214,340] The aPTT therapeutic range should be

established by each institution using regular calibration of the aPTT therapeutic range against UFH levels of 0.3 to 0.7 units/mL (as determined by factor Xa inhibition using a chromogenic assay) or 0.2 to 0.4 units/mL (as determined by protamine sulfate titration) as recommended by the College of American Pathologists (CAP) and ACCP.[181,340,341] Such testing should be performed in the clinical laboratories at each institution according to an institutional SOP, and the aPTT therapeutic range should be printed on the laboratory report. In the event that this information is unavailable, a fixed aPTT therapeutic range of 2 to 2.5 times the baseline aPTT for the patient is recommended by the panel to monitor UFH dosing. Monitoring is generally not performed in patients receiving prophylactic doses of subcutaneous UFH.[338]

LMWHs and Fondaparinux

LMWHs act by potentiating the inhibitory activity of antithrombin against factor Xa and, to a lesser extent, thrombin.[181] Fondaparinux is a synthetic indirect factor Xa inhibitor that also functions through potentiation of antithrombin activity.[159] Measurement of factor Xa inhibition, not the aPTT, is necessary to monitor the anticoagulant effect of LMWH or fondaparinux, because thrombin inhibition associated with LMWH or fondaparinux is weak or absent, respectively.[159,181] However, only limited data are available on the use of factor Xa inhibition to monitor and adjust LWMH or fondaparinux therapy, and monitoring of patients receiving LMWH or fondaparinux is generally not performed because of the more predictable dose response associated with these agents.[181,200] As previously discussed, LMWH should be used with caution in patients with renal dysfunction; the prescribing information for specific agents should be followed for renal dysfunction and body-weight dosing. Dose adjustments should be considered in patients with severe renal dysfunction (C_{cr} <30 mL/min). LMWH anti-Xa monitoring (peak and trough) has been recommended for patients with severe renal dysfunction, although only limited data are available to support the clinical relevance of anti-Xa levels.[181,194,342] A meta-analysis of studies in patients treated with LMWH (enoxaparin in the large majority of studies) showed that anti-Xa levels were significantly elevated among patients with severe renal dysfunction (C_{cr} ≤30 mL/min) compared with those with C_{cr} >30 mL/min, and that risks of major bleeding were increased in the former subgroup.[194] These effects were found when therapeutic doses of enoxaparin were used, but not with prophylactic doses. If anti-Xa levels are monitored in LMWH-treated patients, it is recommended that chromogenic methods be used.[342] In general, the panel recommends limiting the use of LMWHs and fondaparinux in patients with renal insufficiency and those at extremes of body weight, rather than close monitoring. Panel opinions diverged on the utility of measuring factor Xa inhibition in certain cases, such as in patients with very high body weight (>150 kg) receiving LMWH for an extended period of time.

Direct Thrombin Inhibitors

Argatroban and bivalirudin are parenteral DTIs that do not require antithrombin for anticoagulant activity. Therefore, the anticoagulant effect of these agents can be measured using the aPTT, although results can be affected by the specific DTI and the aPTT assay reagents used.[338] Target aPTT ratio ranges of 1.5 to 3 times control and 1.5 to 2.5 times control are recommended when using argatroban and bivalirudin, respectively (see Guidelines section on Therapeutic Options for *Heparin-Induced Thrombocytopenia [HIT]*). As argatroban is metabolized in the liver,[343] significant dose reductions are necessary in patients with impaired liver function; argatroban should be avoided in patients with severely impaired hepatic function.

A third thrombin inhibitor, desirudin, is currently unavailable in the United States.

Dabigatran is a DTI indicated for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.[344] Dabigatran levels can be measured using the Hemoclot® thrombin inhibition test (a dilute thrombin time) or the ecarin clotting time, but monitoring is generally not necessary to guide therapy. The aPTT is relatively insensitive to dabigatran (approximately 2-fold prolongation at peak levels post-dosing and 1.5-fold prolonged at trough levels) and the sensitivity of the aPTT to dabigatran can vary depending on the reagents and coagulometers employed.[345] However, the aPTT can be used to gain a rough idea of whether dabigatran is present. The half-life of dabigatran in healthy subjects is 12 to 17 hours.[344] According to the manufacturer, the concomitant use of dabigatran with P-glycoprotein (P-gp) inducers (eg, rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.[344] For patients with C_{cr} >30 mL/min, the manufacturer recommends a dose of 150 mg orally, twice daily.[344] No dose adjustment of dabigatran is recommended in patients with mild or moderate renal impairment. For patients with C_{cr} 15 to 30 mL/min, the recommended dosing is 75 mg orally, twice daily.[344] Recent reports of bleeding complications in patients taking dabigatran have noted that reduced renal function (C_{cr} <50 mL/min), lower body weight (<60 kg), and older age (≥80 years) were associated with an increased risk of bleeding complications.[346,347] Since there is no antidote to dabigatran should bleeding occur, it should be avoided in patients with reduced renal function, lower body weight, and advanced age. Because dabigatran has not been tested in cancer patients, the NCCN Panel currently does not recommend its use for therapeutic or prophylactic anticoagulation or for the management of HIT in patients with cancer.

Warfarin

Warfarin inhibits production of functional forms of vitamin K-dependent anticoagulation factors, such as factors II, VII, IX, and X as well as the endogenous anticoagulant proteins, protein C and protein S, by the liver.[219] Warfarin dose requirements are highly variable and influenced by a large number of factors, including individual genetic factors (polymorphisms of the vitamin K epoxide reductase and CYP2C9 genes), vitamin K intake, use of medications that influence warfarin and vitamin K metabolism, and liver function. Therefore, close monitoring of the INR (ratio of PT to the mean normal PT normalized for PT reagent sensitivity to warfarin-induced reductions in vitamin K-dependent coagulation factors) is required to determine the therapeutic warfarin dose for an individual patient.[338] The panel recommends a target INR of 2 to 3 for VTE treatment, which is consistent with ACCP recommendations.[183] Initially, the INR should be checked at least twice weekly during the transition phase from concurrent therapy with a parenteral anticoagulant (UFH, LMWH, or fondaparinux) to warfarin monotherapy. Once stable INRs are achieved, monitoring can be gradually decreased in frequency in a step-wise fashion from once weekly to once monthly. Dose changes, addition of new medications--particularly medications with the potential to interact with warfarin—or changes in clinical status should prompt more frequent monitoring. A recent multicenter randomized clinical trial demonstrated that computer-assisted dosing of warfarin was superior to dosing directed by experienced providers.[348] Therefore, use of computer-assisted dosing should be considered in the management of patients on chronic warfarin therapy. Care should be used when making the transition from a DTI to warfarin in the management of HIT, because all of the DTIs prolong the INR to a varying degree (the strength of this effect is: argatroban > bivalirudin > lepirudin)[181,338,349,350]; and the duration of this effect is extended in argatroban-treated patients with hepatic dysfunction[343] (see Guidelines section *Therapeutic Options for Heparin-Induced Thrombocytopenia [HIT]*).

Related Issues in VTE Prophylaxis and Treatment

Reversal of Anticoagulant Activity

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).[157,158,160,351] This agent must be used with caution because it can cause severe hypotension or anaphylactoid reactions, particularly if infused more rapidly than 5 mg per minute.[157,158,160,161,181,351-353] Patients with fish allergies, previous exposure to protamine (eg, NPH insulin), or vasectomized or infertile men are at increased risk for allergic reactions[181,352] (see Guidelines section *Reversal of Anticoagulation*).

The management of patients with a supratherapeutic INR while treated 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 K1 for patients who are thought to be at higher risk of bleeding.[219,354-356] It should be noted that a randomized placebo-controlled trial of 1.25 mg oral vitamin K versus placebo for INR reversal in asymptomatic patients (with an INR of 4.5–10) did not demonstrate any reduction in bleeding or thromboembolic complications.[357] Of note, only 8% of the participants had active cancer. 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 greater than 10 on warfarin, and who have no evidence of bleeding.[356] Patients with an INR ranging up to 10 on warfarin, and who have no evidence of bleeding, should have their warfarin dose held, but the routine use of vitamin K is not warranted in these cases.[356] It is prudent to review potential drug and/or dietary interactions so that the effects of such interactions can be eliminated or taken into account for future warfarin dosing. After withholding/reducing the warfarin dose and administering vitamin K1 as needed, the INR should be monitored closely—daily for inpatients and every 1 to 2 days for outpatients. When INR approaches therapeutic levels (INR <4), warfarin may be restarted at reduced doses if a causal factor cannot be identified or eliminated. INR should then be rechecked after 4 to 7 days, and warfarin dose should be adjusted based on weekly INR measurements until stable therapeutic levels are obtained.

For patients requiring rapid warfarin reversal for urgent or emergent surgical procedures, IV administration of vitamin K1 may be preferred over oral vitamin K1. In a prospective randomized study that compared INR outcomes with IV (0.5 mg) or oral (2.5 mg) vitamin K1 in patients with baseline INR values of 6 to 10 on warfarin (47 episodes among n=44), 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.[358] In a recent prospective study that evaluated vitamin K1 in patients requiring rapid warfarin reversal for elective surgery (n=178), IV vitamin K1 (3 mg; given 12–18 hours prior to procedure) resulted in INR ≤1.5 on the day of surgery in nearly all patients (94%).[359] Thus, for patients on warfarin requiring reversal within 24 hours of surgery, IV vitamin K1 (1–2.5 mg over 1 hour) is recommended. INR assessment should be repeated prior to surgery to determine the need for supplemental reversal agents such as fresh frozen plasma (FFP). For patients requiring reversal within 48 hours of surgery, 2.5 mg of oral vitamin K1 can be given. For these cases, INR measurements should be repeated 24 hours prior and immediately prior to surgery to determine the need for additional vitamin K or FFP (see Guidelines section *Reversal of Anticoagulation*).

The patient with serious or life-threatening bleeding requires 10 mg of IV vitamin K1 and the 4-factor prothrombin complex concentrate (4-factor PCC).[354,360] Close monitoring of INR is required. If 4-factor PCC is

unavailable or the patient is allergic to heparin or had experienced HIT within a year, 3-factor PCC may be used. Other alternatives include FFP and rhFVIIa. Administration of IV vitamin K1 alone is insufficient in such a critical situation because it requires at least 4 to 6 hours to begin to reduce the INR.[361] Since warfarin acts by inhibiting production of functional vitamin K-dependent clotting factors (factors II, VII, IX, and X) as well as protein S and protein C, the administration of a 4-factor PCC containing therapeutic quantities of factors II, VII, IX, and X can facilitate the rapid reversal of its anticoagulation effect.[360] FFP alone can be given in place of PCC plus FFP if PCC is not available, but a disadvantage of this approach is the time delay associated with the preparation, delivery, and infusion of FFP.[351,362] RhVIIa can also be used to rapidly reverse warfarin in place of either FFP or PCC.[354,363,364] There is a small risk for anaphylaxis (3 per 10,000) associated with the IV administration of vitamin K1, especially when it is administered more rapidly than 1 mg per minute,[351,365] and PCC and rhFVIIa have been associated with a low risk for thromboembolic events.[366,367]

Specific agents to reverse many of the newer anticoagulants do not exist. There is less evidence to guide the management of patients treated with these drugs in need of anticoagulant reversal. Nevertheless, IV rhFVIIa, which rapidly induces thrombin generation, has been shown to reduce the anticoagulant effects of LMWHs, DTIs, and fondaparinux in laboratory tests.[181,351,364,368-373] Although evidence from published studies are limited, available data from *in vitro* models and healthy volunteers support the use of rhFVIIa for management of severe bleeding events with fondaparinux.[181,368-370] For DTIs, activated PCC (APCC) such as FEIBA has been evaluated as a potential option for reversing the effects of DTIs by improving hemostatic capacity.[374-376] It is important to note that rhFVIIa and APCC have been associated with thromboembolic events,[372,377] and therefore require caution when employing these agents as potential reversal agents. Other proposed strategies for reversal of DTIs include administration of FFP or cryoprecipitate; use of desmopressin acetate (DDAVP), which stimulates release of factor VIII and von Willebrand factor; and antifibrinolytic agents, which block plasmin activity (ie, the enzyme which breaks down fibrin clots).[351,378-383] It is important to remember that DDAVP is effective only for 3 or 4 doses after which tachyphylaxis develops (see Guidelines section on *Reversal of Anticoagulation*).[384,385] Although rare, DDAVP has also been associated with hyponatremia.[384] The DTI dabigatran is primarily excreted in the urine and shows low plasma protein binding (approximately 35% bound to human plasma proteins). Thus, dabigatran can be dialyzed with the removal of about 60% of drug over 2 to 3 hours, although clinical data supporting this approach are limited.[344,345,386,387] APCC and rhFVIIa have been suggested as reversal agents for dabigatran, as with other DTIs.[387,388] Activated charcoal may also be considered for reversal of dabigatran, especially within a few hours of overdose.[345,389]

As with the newer anticoagulant agents mentioned above, no specific reversal agent currently exists for the direct factor Xa inhibitors rivaroxaban and apixaban.[390] The prescribing information indicates that activated charcoal may be considered for reduction of drug absorption.[204,208] Due to the high plasma protein binding, these agents are not expected to be dialyzable. Limited data from *in vivo* models and healthy volunteers suggest that PCC may at least partially reverse the anticoagulation effects.[391,392] The use of rhFVIIa may also be considered, although data are presently unclear in terms of its benefits.[388,389,393]

Failure of Anticoagulation Therapy

Anticoagulation failure is defined as extension of DVT or PE, or new DVT or PE, while on recommended anticoagulation therapy (see Guidelines section on *Therapeutic Anticoagulation Failure*).[394] Although there are many potential causes of anticoagulation therapy failure, an initial determination of whether the INR or aPTT is within the therapeutic range

is important for patients with recurrent VTE who are receiving warfarin or UFH, respectively. When INR or aPTT values are subtherapeutic, one obvious option is to increase the anticoagulant dose to a therapeutic level.

Although anticoagulation therapy failure for patients receiving warfarin, UFH, LMWH, or fondaparinux can result if the prescribed anticoagulant dose is inadequate, other factors to consider include patient adherence to self-administered medications, such as an oral vitamin K antagonists, or subcutaneously administered anticoagulants, and the dosing frequency for patients receiving LMWH.[394] For example, an increased risk for VTE recurrence was reported in one study of cancer patients receiving once-daily enoxaparin in the acute therapy setting.[395] Thus, a twice-daily dosing schedule is an option for patients exhibiting recurrent VTE while receiving once-daily therapy with an LMWH. A dose increase can also be considered for patients exhibiting recurrent VTE while receiving anticoagulant therapies for which anticoagulant effects are not typically monitored in the laboratory (eg, LMWH and fondaparinux).[396]

INR or aPTT values may be subtherapeutic in situations where inadequate anticoagulant dosing is not the direct cause of recurrent VTE. For example, warfarin resistance (inability to achieve a therapeutic INR on warfarin doses typically used to treat VTE) can be due to genetic variability associated with the enzymatic metabolism of warfarin, or the concomitant administration of medications that interact with warfarin.[397,398] An option for patients undergoing warfarin therapy and exhibiting a subtherapeutic INR is a switch to intravenous LMWH (preferred), intravenous UFH, or fondaparinux. A switch to LMWH in the setting of a 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 failure of warfarin therapy.[399] Likewise, heparin resistance (inability to achieve therapeutic aPTT on heparin doses typically used to treat VTE), though rare, can occur as a result of pharmacokinetic or biophysical/physiologic limitations of heparin therapy.[400]

Anticoagulation failure of warfarin or UFH can also occur in the setting of a therapeutic INR or aPTT value. Causes include cancer-related hypercoagulability such as the Trousseau's syndrome, HIT, cancer-related anatomic causes such as vascular compression, and acquired and/or familial thrombophilia.[394,400] Diagnostic testing to identify syndromes identified above, when present, is critical to the management of VTE in these patients.[394] In patients with anatomic compression due to congenital (eg, May-Thurner syndrome or iliac vein compression syndrome, thoracic outlet syndrome) or acquired causes (vascular compression by nodal or tumor masses), relief of anatomic compression is essential to preventing recurrent thrombosis. Clinical suspicion of HIT should be high when recurrent VTE is observed in a cancer patient receiving heparin-based therapy or in a patient who received such therapy in the recent past. Options for patients with VTE recurrence while receiving UFH characterized by a therapeutic aPTT level include a switch to intravenous LMWH or fondaparinux or an increase in the dose of intravenous UFH. Likewise, patients with recurrent VTE and a therapeutic INR while on warfarin therapy can be switched to intravenous heparin (LMWH preferred) or fondaparinux. A switch to heparin-based therapy is an option following failure of fondaparinux to prevent VTE recurrence and vice versa.

Placement of an IVC filter is an option for treating patients with PE or progression of central DVT despite therapeutic anticoagulation with UFH, LMWH, or fondaparinux, although filters should be avoided in the setting of HIT or migratory thrombophlebitis due to the systemic nature of these coagulopathies.[98,99]

Perioperative Management of Anticoagulation and Antithrombotic Therapy

Management of surgery-associated bleeding in cancer patients is complicated by the need of anticoagulation in many of these patients due to thetheir malignancy, cancer therapy, and/or comorbidities. A balance of the thrombotic risk and bleeding risk is important. An IVC filter should be considered if VTE occurred within 1 month of planned surgery. Bridging anticoagulation therapy refers to the use of short-acting anticoagulants (LMWH or UFH) for 10 to 20 days during the peri-procedural period.[401]

Cancer patients on anticoagulants requiring emergent surgery should be managed according to the Guidelines section *Reversal of Anticoagulation in the Event of Life-threatening Bleeding or Emergent Surgery*.

If the surgical procedure is non-emergent, an assessment of the bleeding risk should be performed before the procedure. To date, a consensus has not been reached on the optimal preoperative screening strategy.[401] Guidelines on estimating bleeding risk based on the type of surgical procedure are listed in Table 1 of the Guidelines section *Perioperative Management of Anticoagulation and Antithrombotic Therapy*. Patients assessed to be at very low risk of bleeding can continue anticoagulation and undergo surgery. All other patients should then be assessed for thromboembolic risk according to Table 3 of the same Guidelines section. In general, anticoagulation therapy should be stopped before surgery for these patients. Bridging anticoagulation therapy should be administered for patients at high thrombotic risk and considered for patients at moderate thrombotic risk. Panel recommendations on anticoagulation before and after surgery based on both the bleeding and thrombotic risks are detailed in Table 2.

Diagnosis and Management of HIT

Specific guideline recommendations regarding HIT are available from the ACCP.[202,402] HIT is caused by a relatively common immunologic reaction to heparin-based products. In one pharmacy-based surveillance study, 0.2% of patients receiving heparin therapy developed HIT, although the incidence of HIT was 1.2% in patients exposed to heparin for more than 4 days.[403] In another study, 2.7% of patients treated with UFH developed HIT.[404] HIT is triggered when UFH (or to a lesser extent LMWH) bind to platelet factor 4 (PF4) released by activated platelets and form an immunogenic PF4-heparin complex leading to the development of antibodies. These antibodies increase platelet clearance and activate platelets, resulting in the release of procoagulant microparticles and increased thrombin generation.[202,405] The end result is a consumptive thrombocytopenia and profound prothrombotic state that triggers symptomatic thromboembolism in as many as 75% of patients.[202,405] Clinical evidence of HIT includes development of thrombocytopenia, formation of necrotic lesions at injection sites, arterial thromboembolic complications, and/or development of VTE.[406,407] Most typically, HIT occurs after 5 to 10 days following initial exposure to heparin-based products. In rapid-onset HIT, 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.[202] Delayed-onset HIT is less common, and can occur days or weeks after heparin therapy has been discontinued.[405]

Some evidence indicates that cancer patients are at increased risk of developing HIT and HIT-related VTE,[408,409] although this has not been firmly established. HIT has been associated with the use of both LMWHs and UFH. Increased rates of HIT have been observed in patients receiving heparin-based therapy who were previously exposed to such therapy.[410] Results of some studies have indicated that the frequency of HIT with LMWH and UFH is similar,[410,411] whereas other studies suggest a lower incidence of HIT in patients receiving LMWH relative to those receiving

UFH.[404,412-414] It has been suggested that factors such as anticoagulant dose (lower with prophylactic doses, higher with treatment doses) and whether the patient is treated in the medical (lower-risk) or surgical (higher-risk) setting may account for these conflicting results, since a lower relative incidence of HIT with LMWH was primarily observed for surgical patients receiving prophylactic doses of anticoagulant therapy.[415]

A diagnosis of HIT is based on both clinical and serologic evidence.[202] Hence, the presence of both clinical sequelae of HIT, including thrombosis and thrombocytopenia defined as a drop in platelet count by more than 50%, and anti-PF4/heparin antibodies are needed for a diagnosis. Furthermore, 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. As mentioned by Greinacher et al, "all HIT is caused by platelet activating antibodies, but not all PF4/heparin antibodies cause HIT."[416] 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 detect the presence of HIT antibodies, but do not assess their ability to activate platelets.[202]

The diagnosis of HIT is complicated by the high frequency of heparin use in hospitals; the presence of HIT antibodies, which do not activate platelets; possible delays in obtaining serologic test results; and multiple 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.[416]

The 4Ts score is a simple, validated tool designed to assess the probability of HIT based on specific characteristics of 4 clinical parameters: **t**hrombocytopenia; the **t**iming of the onset of platelet fall; the presence of **t**hrombosis or other clinical sequelae; and evidence of o**t**her potential causes of thrombocytopenia (see Guidelines section *HIT Pre-test Probability Score Assessment*).[417-419] Each of these 4 parameters is weighted by a score of 0 to 2 according to how likely it reflects a HIT diagnosis. A total score of 0 to 8 is possible. Total scores are grouped into 3 categories, which classify the patient as being at low- (0–3), medium- (4–5), or high-risk (6–8) of HIT.[419] As described above for HIT antibody testing, 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.[418,420] Cuker and colleagues[421] developed an alternative pre-test probability model based on broad expert opinion of HIT diagnosis known as the HIT Expert Probability score (HEP score). In a validation patient cohort, the HEP score demonstrated greater inter-observer reliability and correlation with laboratory test results and expert assessment of the probability of HIT diagnosis than the 4T score.[421] Neither HIT pre-test probability model has been assessed in an oncology-specific population.

The panel recommends platelet monitoring at baseline and then every 2 to 3 days for at least the first 14 days, and then every 2 weeks thereafter, or more frequently as clinically indicated, in patients receiving anticoagulation therapy with UFH or LMWH. If HIT is suspected, the patient should be evaluated using the 4Ts score. Recommendations for patients classified as being at low risk for HIT include the following: consider alternative causes of thrombocytopenia; weigh the risks/benefits of continued therapy with heparin versus a DTI or fondaparinux; consider maintaining anticoagulation with heparin; monitor their clinical status; and consider HIT antibody testing by ELISA in select patients based on clinical judgement. Patients classified as being at moderate/high risk for HIT on the basis of the 4Ts score should initially be managed as having a diagnosis of HIT. HIT antibody testing by ELISA should be ordered, although immediate discontinuation of heparin-based products and administration of an alternative anticoagulant, typically a DTI, is recommended. Warfarin should be discontinued and reversed with vitamin K. The safety of platelet

transfusions in patients with HIT remains controversial. Platelet transfusions may be considered for clinically significant bleeding or prior to invasive procedures in patients with a platelet count less than 50,000/mcL. Prophylactic platelet transfusions are otherwise not recommended because of the theoretic risk of triggering further thrombosis.

The results of HIT antibody testing by ELISA further direct management. For example, options for patients with a negative HIT antibody test result include a reassessment of anticoagulation therapy based on the 4Ts score, and consideration of repeat HIT antibody testing if the pre-test probability of HIT is moderate to high. A diagnosis of HIT can be ruled out in those patients with a negative HIT antibody test on repeat testing. The management of patients with a positive HIT antibody test on initial testing should be re-evaluated based on the 4Ts score pre-test probability. Patients with a moderate/high 4Ts score should be managed according to recommendations for patients with a diagnosis of HIT, whereas SRA testing should be considered in those with a low pre-test probability with test results directing further management. A 4-extremity duplex ultrasound may be considered in confirmed HIT case to identify sub-clinical DVT.

Anticoagulants for the Treatment of HIT

Direct Thrombin Inhibitors

DTIs available for the management of HIT include argatroban and bivalirudin.[202] Two prospective clinical trials evaluated the activity of argatroban in patients with clinically diagnosed HIT, with or without concurrent thrombosis.[422,423] In the initial trial, argatroban significantly reduced the combined endpoint of death, limb amputation, and occurrence of new thrombotic events among patients with HIT without thrombosis (n=160), 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 (n=144).[422] 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 (n=189) (28.0% vs. 38.8%; *P* = .04), but not in patients with HIT and thrombosis (n=229) (41.5% vs. 56.5%; *P* = .07).[423] 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), in both groups of patients with HIT with or without concurrent thrombosis.[422,423]

Argatroban is approved by the FDA for the immediate treatment of HIT.[343] Argatroban is primarily metabolized by the liver, and prolonged clearance of this agent has been seen in patients with hepatic insufficiency.[343] Therapeutic dosing regimens of many anticoagulants used in the treatment of critically ill patients with organ dysfunction and HIT are often lower than those recommended by the manufacturer and require frequent monitoring. The manufacturer-recommended dose for argatroban may be too high, especially for the treatment of HIT in critically ill patients.[424-426] Argatroban administered at a reduced dose of 1 mcg/kg/min may be adequate to provide sufficient anticoagulation.[426] Dose reductions have also been suggested for bivalirudin,[427] another DTI, when used off-label in the treatment of HIT[428] and in patients with HIT and hepatic and/or renal insufficiency or critically ill patients.[350,429,430] Although some of the pharmacologic characteristics of bivalirudin, including HIT short half-life and enzymatic metabolism, are advantageous in the setting of HIT, data regarding its use in HIT are limited.[350]

Dabigatran is a DTI approved by the FDA for the reduction of risk for stroke and systemic embolism in patients with non-valvular atrial fibrillation.[344] This agent is not approved for the treatment of HIT, and the NCCN Guidelines Panel for VTE does not currently recommend the use of dabigatran in patients with cancer.

The panel recommends a DTI as the preferred treatment for the immediate management of HIT. 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 for the immediate treatment of HIT should be a consideration in the choice of therapy. Use of argatroban should be avoided in patients with hepatic failure and severe renal insufficiency, respectively.

Fondaparinux

The option of off-label use of fondaparinux as an alternative to parenteral DTIs in the treatment of a current episode of HIT without thrombosis is also included in the NCCN Guidelines for VTE.[431] Advantages to the use of fondaparinux in this setting, in addition to subcutaneous administration, include its lack of INR prolongation when administered concomitantly with warfarin. Although the long half-life of fondaparinux is a disadvantage in situations where anticoagulation reversal is necessary, a possible benefit may include a decreased risk for rebound hypercoagulability.[432] Furthermore, unlike DTIs, aPTT testing is not used to monitor treatment response of fondaparinux, thereby eliminating problems associated with warfarin prolongation of the aPTT when overlapped with a DTI. Fondaparinux has been used in small numbers of patients with HIT and generally appears to be safe.[433-435] There have been rare reports of an association between fondaparinux use and development of HIT, although in most cases patients had prior exposure to UFH or LMWH.[436-439] It has been suggested that use of fondaparinux for patients with HIT and without a contraindication to fondaparinux be restricted to those who have recovered from a recent episode of HIT without thrombosis and are ready to be discharged from the hospital, but who are not yet stable on warfarin therapy.[202,432] Fondaparinux is included in the guidelines as a category 2B option for the immediate management of HIT.

Warfarin

The panel recommends against the use of warfarin therapy in patients with a moderate or high pre-test probability of HIT by the 4T score. For patients receiving warfarin, it should be discontinued and reversed with vitamin K.[202] 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, which can result from warfarin-induced reductions in protein C levels in the setting of profound activated coagulation due to HIT.[202,440] After platelet recovery (≥150,000/mcL or when platelets return to baseline), 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, co-administration of a DTI and warfarin produces a combined effect on the 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. Argatroban in particular, but also other DTIs, can prolong the INR during co-therapy with warfarin. Since argatroban has the lowest affinity for thrombin of the 3 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.[349,441] A higher target INR should therefore be achieved before argatroban is discontinued.[202,343,441] Once DTI is discontinued, a repeat INR and aPTT should be obtained 2-6 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.[442,443] The duration of warfarin therapy is dependent on whether HIT is accompanied by thrombosis. In patients with HIT and thrombosis, the duration of therapy is dictated by the nature of the thrombotic event (3 months for DVT, 6 months for PE). In patients with HIT

without thrombosis, at least 1 month of warfarin therapy is recommended.[405]

Withholding Anticoagulation Therapy: Elements to Consider in the Decision Not to Treat

The feasibility of invasive or aggressive intervention is not the only consideration for VTE prophylaxis and treatment in cancer patients.[444] The risks and probability of success of the interventions should be considered as well. Factors to consider before implementing anticoagulation therapy include patient refusal; lack of therapeutic advantage; lack of palliative benefits; and whether anticoagulation is associated with an unreasonable burden. Likewise, careful consideration of these issues is also very important in deciding to withhold or withdraw VTE therapy.

Summary

Recognizing the increased risk for VTE in cancer patients is the first step in preventing the occurrence of VTE and promptly identifying VTE in these patients. The NCCN Guidelines Panel recommends VTE thromboprophylaxis for all hospitalized patients with cancer who do not have contraindications to such therapy, and the panel also emphasizes that an increased level of clinical suspicion of VTE should be maintained for cancer patients. Following hospital discharge, it is recommended that cancer patients in a high-risk setting for VTE continue to receive VTE prophylaxis, with the duration of anticoagulation determined by the clinical situation. Careful evaluation of cancer patients in whom VTE is suspected and prompt treatment and follow-up for patients diagnosed with VTE is recommended after the cancer status of the patient is assessed and the risks and benefits of treatment are considered.

Patient Resources for VTE Management

Websites:

- National Blood Clot Alliance - www.stoptheclot.org
- ClotCare Online Resource - http://www.clotcare.com/
- North American Thrombosis Forum - http://natfonline.org/patients
- Clot Connect - http://www.clotconnect.org/patients
- Living with Thrombophilia - http://fvleiden.org/index.html

Related Materials:

- Preventing deep vein thrombosis (American College of Obstetricians and Gynecologists) - http://www.acog.org/~/media/For%20Patients/faq174.pdf?dmc=1&ts=20140618T1232288986
- Deep vein thrombosis (American Academy of Family Physicians) - http://familydoctor.org/familydoctor/en/diseases-conditions/deep-vein-thrombosis.html
- Deep vein thrombosis (National Heart, Lung, and Blood Institute) - http://www.nhlbi.nih.gov/health/health-topics/topics/dvt/
- Deep vein thrombosis (MedLinePlus) - http://www.nlm.nih.gov/medlineplus/deepveinthrombosis.html
- Deep vein thrombosis/pulmonary embolism (Centers for Disease Control and Prevention) - http://www.cdc.gov/ncbddd/dvt/facts.html
- Your guide to preventing and treating blood clots (Agency for Healthcare Research and Quality) - http://www.ahrq.gov/patients-consumers/prevention/disease/bloodclots.html

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