National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Venous Thromboembolic Disease

V.1.2009

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This manuscript is being updated to correspond with the newly updated algorithm.

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

To find clinical trials online at NCCN member institutions, go to www.nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines updates

Summary of major changes in the 1.2009 version of the Venous Thromboembolic Disease guidelines from the 2.2008 version include:

(VTE-1)

- The phrase "Relative contraindication to anticoagulation..." was changed to "Contraindication to anticoagulation" throughout the guidelines.
- "Pneumatic venous compression device (VCD)" was changed to "Intermittent pneumatic venous compression device (IPC)".
- "No" pathway: The panel added "± Graduated compression stockings (GSC)."

(VTE-2)

- "Consider VTE prophylaxis...." was changed to "Recommend VTE prophylaxis..."
- Footnotes "f" and "g" are new to the page.

(DVT-1)

- Algorithm title changed to "Deep or Superficial Vein Thrombosis".
- Diagnosis: The following items were added, "Unexplained persistent calf cramping", "Detected radiographically in asymptomatic patients", "Swelling in *face, neck* or....".
- Imaging findings: "Superficial thrombophlebitis" was changed to "Superficial *vein thrombus*" with revised recommendations.
- Continued clinical suspicion of DVT; Yes: "Repeat venous ultrasound" was added under "Venous imaging".

(DVT-2)

- DVT Location: "Superior vena cava" was removed from the Pelvic and Femoral pathway and is now included in the pathway for "Upper extremity".
- Pelvic/iliac/IVC pathway:
  - No: "Graduated Compression Stockings (GCS)" was added.
  - Yes: "Mechanical caval filtering device" changed to "IVC filter". (Also for PE-2)

(DVT-3)

- Catheter required pathway; No:
  - First bullet: "Anticoagulate for as long as catheter is in place and for 1-3 mo after catheter removal" changed to "Anticoagulate... and for at least 3 months after catheter removal".
  - Second bullet: "If symptoms or clot persists, then remove catheter" changed to "If symptoms persist, then remove catheter and anticoagulate for at least 3 months after catheter removal".
  - Resolved pathway: "Anticoagulate for 1-3 mo after catheter removal" changed to "Anticoagulate for at least 3 mo..."
- Catheter not required pathway; No: "Anticoagulate for 1-3 mo" changed to "Anticoagulate for at least 3 mo".

(PE-2)

- Yes; IVC filter: "Follow frequently for change in relative contraindications" was changed to "...for change in clinical status or contraindication to anticoagulation".

Summary of the Guidelines updates

(VTE-A): Risk Factor Assessment

- "Infection" was added as a risk factor.
- Therapeutic agents...: "Oral contraceptives" changed to "Contraceptives". "Growth factors" was removed.

(VTE-B): Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment

- Page title changed to "Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment".
- Seventh Bullet; Underlying coagulopathy: "Factor VIII deficiency" was added as an example of clotting factor abnormalities.

(VTE-C): Inpatient/Outpatient Prophylactic Anticoagulation Therapy

- "Factor Xa antagonist" was changed to "Fondaparinux" throughout the guidelines.
- New footnote "5" regarding tinzaparin and elderly patients was added that states, "Tinzaparin should be avoided in patients over 70 years of age with renal insufficiency. Refer to the FDA website for additional information: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Innohe". (Also for VTE-D)

(VTE-D): Therapeutic Anticoagulation Treatment For Venous Thromboembolism

- Page title changed to "Therapeutic Anticoagulation Treatment For Venous Thromboembolism".
- Stage 1 Immediate:
  - "Stage 1 Immediate: Concomitant with diagnosis or while diagnosis and risk being assessed (heparin phase)" changed to "Stage 1 Immediate: At diagnosis or during diagnostic evaluation".
  - Low-molecular-weight-heparin: New footnote "6" was added that states, "Although each of the low molecular weight heparins (LMWH) have been studied in randomized control trials in cancer patients, dalteparin's efficacy in this population is supported by the highest quality evidence and it is the only LMWH approved by the FDA for this indication."
  - Unfractionated heparin (IV): target aPTT range changed from "2.0-2.9 x control..." to "2.0-2.5 x control..." (Also for VTE-H)

(VTE-D): Therapeutic Anticoagulation Treatment For Venous Thromboembolism:

- Stage 3 Chronic:
  - "Third bullet: "Consider indefinite anticoagulation...." changed to "Recommend indefinite anticoagulation...."
  - Fourth bullet: "For catheter associated thrombosis, anticoagulate as long as catheter is in place and 1- 3 mo after catheter removal" changed to "... anticoagulate as long as catheter is in place and for at least 3 months after catheter removal".

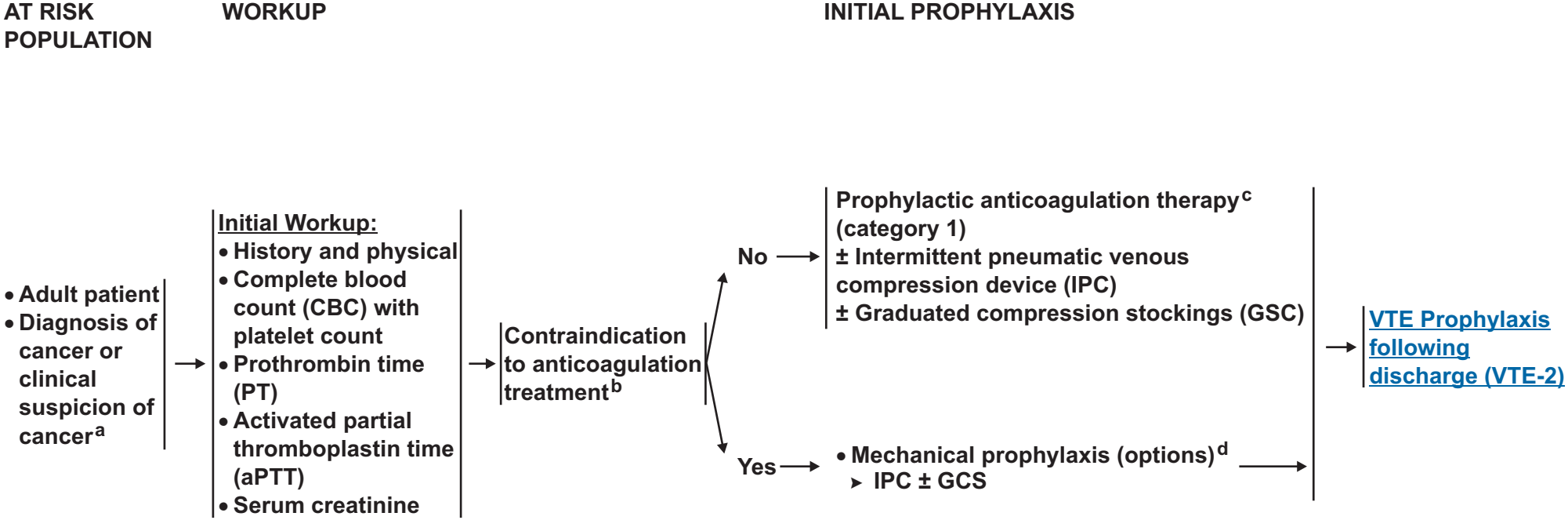
(VTE-G): Diagnosis and Treatment of Heparin Induced Thrombocytopenia

- New bullet "Acute Management" was added.
  - Panel clarified to "Start warfarin at maintenance dose when platelet count recovered..."
  - Third arrow changed to "Platelet transfusions should be avoided unless clinically significant bleeding is present or prior to invasive procedure if already under treatment with a DTI".
- Footnotes "4" and "5" were revised.

(VTE-H): Therapeutic Anticoagulation Failure

- Page title changed to "Therapeutic Anticoagulation Failure".
- Patient on warfarin: "Increase warfarin dose, aiming for therapeutic INR" changed to "Increase warfarin dose and treat with parenteral agent until INR target achieved."
- "Patient on heparin"; Therapeutic aPTT: "Consider placement of IVC filter"and "Consider HIT" were added. (Also for "Patient on LMWH" and "Fondaparinux" pathways.)
- "Patient on LMWH" pathway: "Check LMWH level" was added.
- Fondaparinux pathway: "Check fondaparinux level" was added and "Vitamin K antagonist" was removed.
- Footnotes "1" and "2" were revised.

INPATIENT VENOUS THROMBOEMBOLISM PROPHYLAXIS



[a] See Risk Factor Assessment (VTE-A).
[b] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
[c] Pharmacologic intervention. See Inpatient/Outpatient Prophylactic Anticoagulation Therapy (VTE-C).
[d] Most data come from surgical patients; this is an extrapolation to the medical population.

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VTE PROPHYLAXIS FOLLOWING DISCHARGE

AT RISK POPULATION

- Adult patient
- Diagnosis of cancer
- Patient received VTE prophylaxis during hospitalization
- Cancer inpatient intended for discharge

Cancer surgery patient → **Out of hospital primary VTE prophylaxis is recommended for up to four weeks post-operation (particularly for high-risk abdominal or pelvic cancer surgery patients[e])**
See Inpatient/Outpatient Prophylactic Anticoagulation Therapy (VTE-C)

Medical oncology patient → **Recommend VTE prophylaxis in high risk settings[f,g]**

[e] High-risk abdominal/pelvic cancer surgery patients include patients undergoing surgery for gastrointestinal malignancies, patients with a previous history of VTE, anesthesia time greater than 2 hours, bed rest > 4 days, advanced stage disease and patient age greater than 60 years.
[f] For select patients receiving highly thrombotic antiangiogenic therapy (ie, multiple myeloma patients receiving thalidomide and high-dose dexamethasone).
[g] See Risk Factor Assessment (VTE-A).

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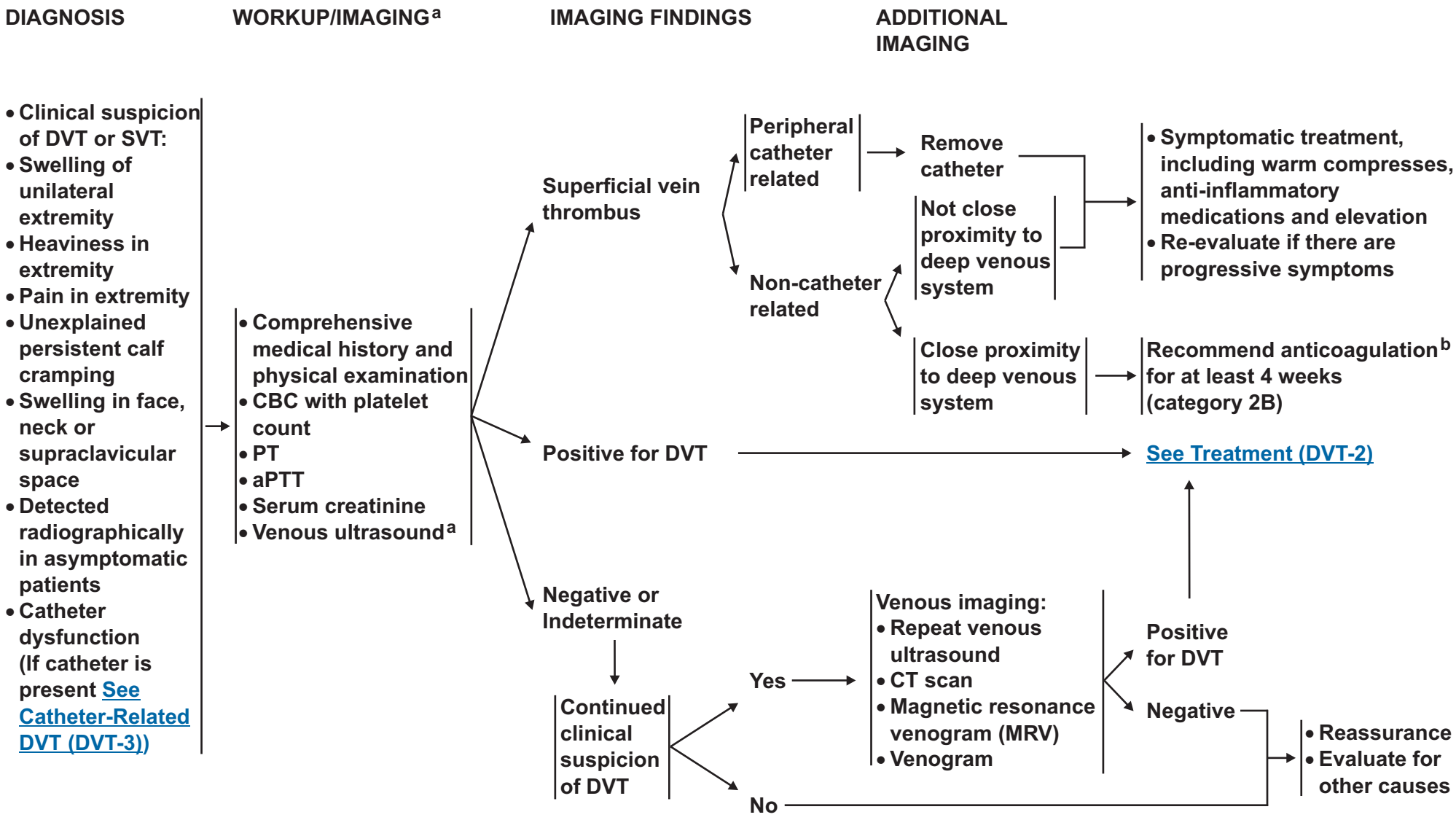
Venous Thromboembolic Disease
Deep or Superficial Vein Thrombosis

DVT/SVT: DIAGNOSIS



[a] Imaging recommendations reflect initial diagnostic workup of an individual who has not previously been diagnosed with DVT.
[b] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (VTE-D).

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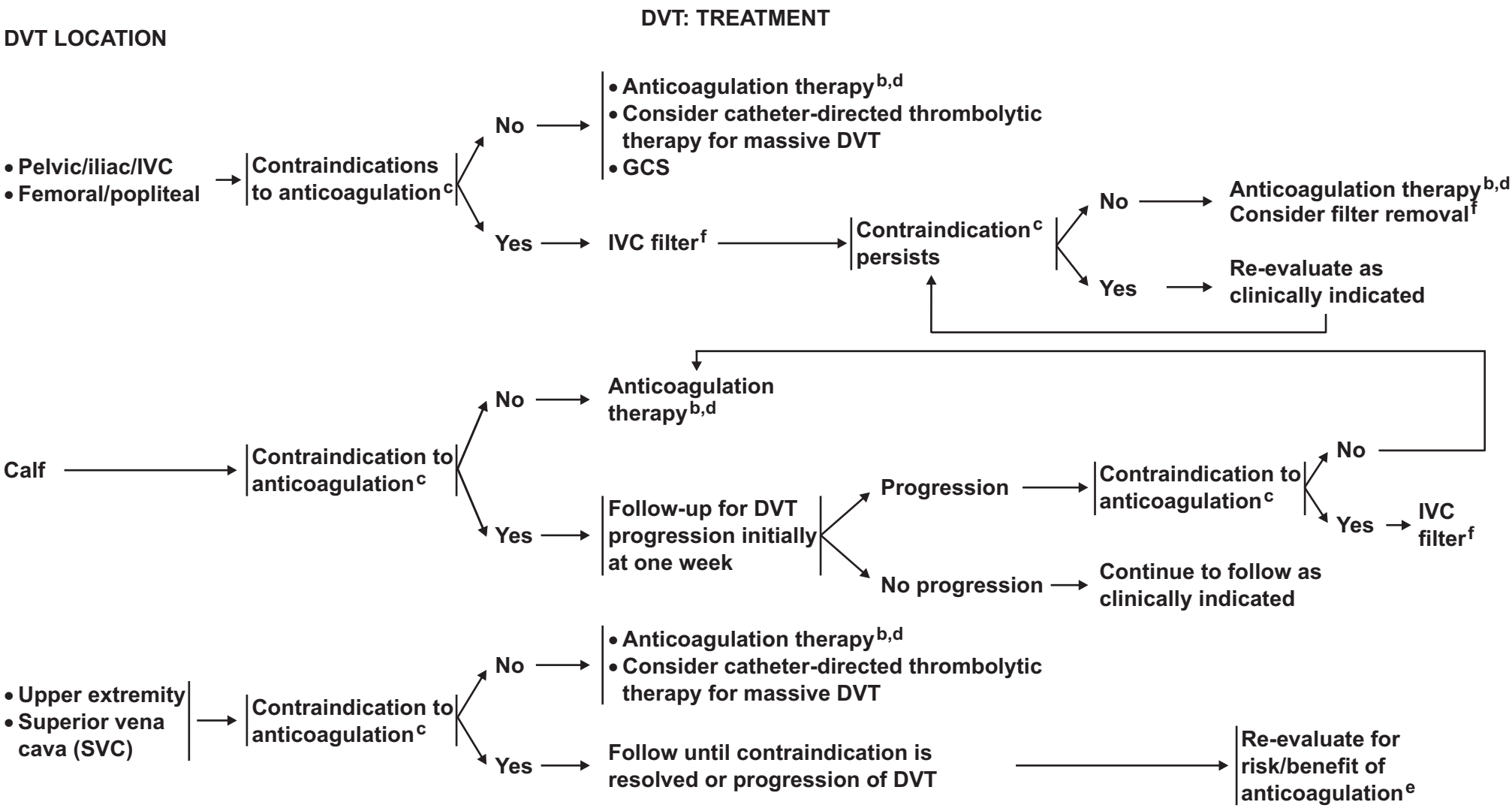
DVT: TREATMENT



[b] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (VTE-D).
[c] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
[d] See Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.
[e] See Elements for Consideration in Decision Not To Treat (VTE-E).
[f] There are retrievable and permanent IVC filters. A permanent filter is preferable if the patient requires an IVC filter >1 mo, for longer than manufacturer's retail recommendation, or the relative risk of bleeding exceeds in vivo time of the retrievable filter.

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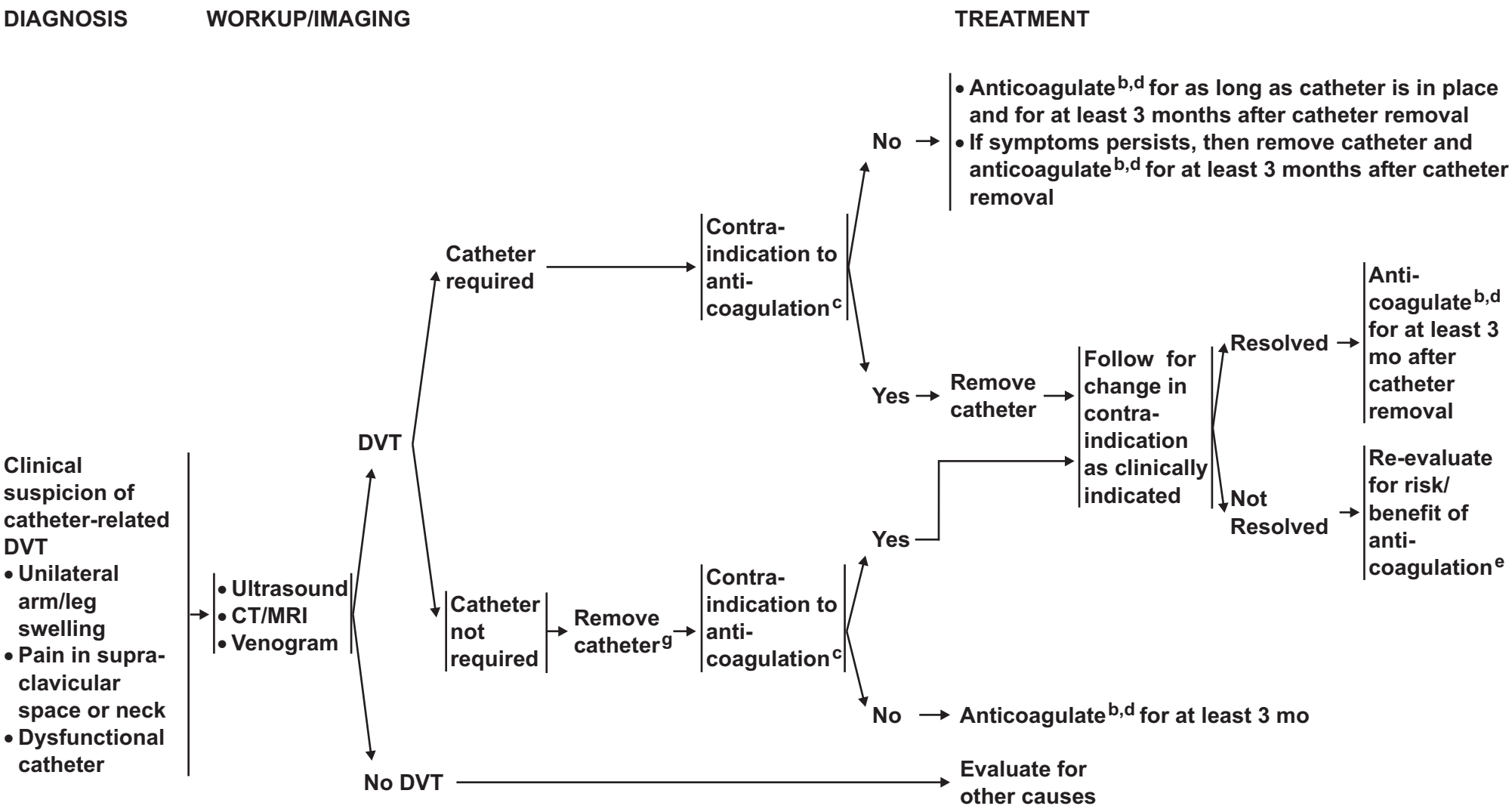
CATHETER-RELATED DVT: DIAGNOSIS



[b] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (VTE-D).
[c] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
[d] See Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.
[e] See Elements for Consideration in Decision Not To Treat (VTE-E).
[g] Consider anticoagulation before catheter removal.

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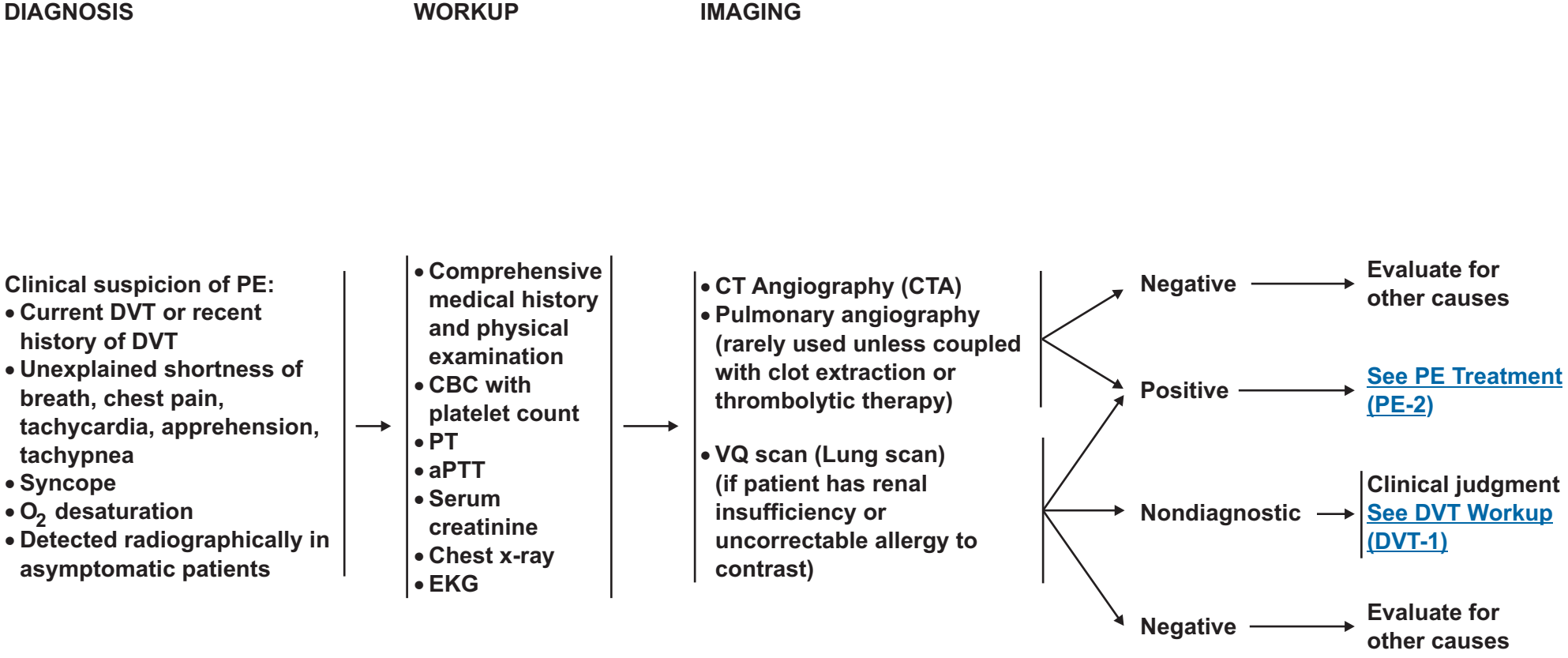
PE: DIAGNOSIS



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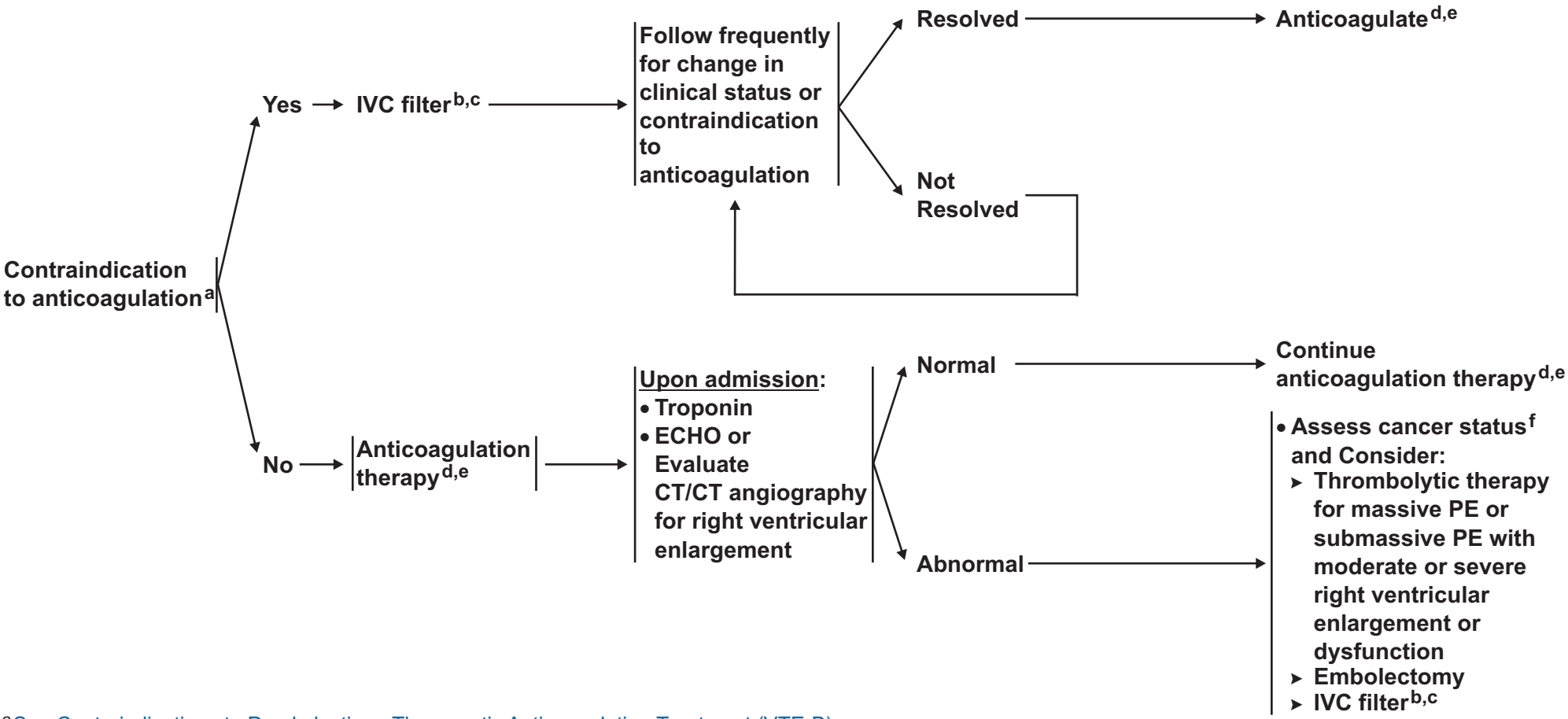
PE: TREATMENT



[a] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
[b] See Clinical Scenarios Warranting Consideration of Filter Placement Indications (VTE-F).
[c] There are retrievable and permanent IVC filters. A permanent filter is preferable if the patient requires an IVC filter >1 mo, for longer than manufacturer's retail recommendation, or the relative risk of bleeding exceeds in vivo time of the retrievable filter.
[d] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (VTE-D).
[e] See Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.
[f] See Elements for Consideration in Decision Not To Treat (VTE-E).

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Venous Thromboembolic Disease

RISK FACTOR ASSESSMENT[1]

- Active cancer
- Age
- Prior VTE
- Familial and/or acquired thrombophilia
- Trauma
- Major surgical procedures
- Acute or chronic medical illness requiring hospitalization or prolonged bed rest
- Central venous catheter/IV catheter
- Congestive heart failure (CHF)
- Pregnancy
- Regional bulky lymphadenopathy with extrinsic vascular compression
- Myeloproliferative disorders
- Infection

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

- Therapeutic agents associated with increased risk:
  - Chemotherapy
  - Exogenous estrogen compounds
    - Hormone replacement therapy (HRT)
    - Contraceptives
    - Tamoxifen/Raloxifene
    - Diethylstilbestrol
  - Thalidomide/lenalidomide plus dexamethasone
  - Erythropoietic stimulation agents

[1] Risk of population for the development of a VTE in a defined time or situation.

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Venous Thromboembolic Disease

CONTRAINDICATIONS TO PROPHYLACTIC OR THERAPEUTIC ANTICOAGULATION TREATMENT

- Recent central nervous system (CNS) bleed, intracranial or spinal lesion at high risk for bleeding
- Active bleeding (major): more than 2 units transfused in 24 hours
- Chronic, clinically significant measurable bleeding > 48 hours
- Thrombocytopenia (platelets < 50,000/mcL)
- Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)
- Recent major operation at high risk for bleeding
- Underlying coagulopathy
  - Clotting factor abnormalities (eg, factor VIII deficiency)
  - Elevated PT or aPTT (excluding lupus inhibitors)
- Spinal anesthesia/lumbar puncture
- High risk for falls

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Venous Thromboembolic Disease

INPATIENT/OUTPATIENT PROPHYLACTIC ANTICOAGULATION THERAPY[1,2,3]

- **LMWH:[4] (category 1 for inpatient)**
  - **Dalteparin 5,000 units subcutaneous daily**
  - **Enoxaparin 40 mg subcutaneous daily**
  - **Tinzaparin[5] 4,500 units (fixed dose) subcutaneous daily or 75 units/kg subcutaneous daily**
- **Fondaparinux[6] (category 1 for inpatient)**
  - **Fondaparinux 2.5 mg subcutaneous daily**
- **Unfractionated heparin: 5,000 units subcutaneous 3 times daily (category 1 for inpatient)**

For Diagnosis and Treatment of Heparin-Induced Thrombocytopenia (HIT), See (VTE-G)

[1] Agent selection based on:
- Renal failure (C_{cr} < 30mL/min)
- FDA approval
- Cost
- Ease of administration
- Monitoring
- Ability to reverse anticoagulation

[2] Follow institutional standard operating procedures (SOP) for dosing schedules, if no SOP then use the American College of Chest Physicians (ACCP) recommendations. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2008;133(6) [suppl]:381S-453S. (www.chestjournal.org)

[3] Following initiation of heparin: Hemoglobin, hematocrit, and platelet count every 2-3 days up to at least day 14 and every two weeks thereafter or as clinically indicated.

[4] LMWHs should be used with caution in patients with renal dysfunction. Dose adjustments and Anti-Xa monitoring may be required. Follow package insert for renal dysfunction and body weight based dosing.

[5] Tinzaparin should be avoided in patients over 70 years of age with renal insufficiency. Refer to the FDA website for additional information: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Innohep

[6] Fondaparinux is contraindicated in patients with creatinine clearance < 30 mls/minute and should be used with caution in patients with moderate renal insufficiency (creatinine clearance 30-50 mls/minute), weight < 50 kg or age > 75 years.

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Venous Thromboembolic Disease

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Discussion, References

THERAPEUTIC ANTICOAGULATION TREATMENT FOR VENOUS THROMBOEMBOLISM[1,2,3,4]

Stage 1 Immediate: At diagnosis or during diagnostic evaluation:

- Low-molecular-weight heparin (LMWH)[5]
  - Dalteparin (200 units/kg subcutaneous daily)[6]
  - Enoxaparin (1 mg/kg subcutaneous every 12 hours)
  - Tinzaparin[7] (175 units/kg subcutaneous daily)
- Fondaparinux[8] (5 mg [< 50 kg]; 7.5 mg [50-100 kg]; 10 mg [> 100 kg] subcutaneous daily)
- Unfractionated heparin (IV) (80 units/kg load, then 18 units/kg per hour, target aPTT of 2.0-2.5 x control or per hospital SOP)

Stage 2 Acute: Short term, during transition to chronic phase:[1]

- LMWH[5] (category 1) is preferred as monotherapy without warfarin in patients with proximal DVT or PE and prevention of recurrent VTE in patients with advanced or metastatic cancer
- If UFH or Factor Xa antagonist, transition to LMWH or warfarin
- Warfarin[2] (2.5-5 mg every day initially, subsequent dosing based on INR value; target INR 2.0-3.0)[9]

Stage 3 Chronic: Duration as recommended by guideline:

- LMWH[5] (category 1) or Warfarin (adjusted for INR 2.0-3.0)[9]
- Minimum time of 3-6 mo for DVT and 6-12 mo for PE
- Recommend indefinite anticoagulation if active cancer or persistent risk factors
- For catheter associated thrombosis, anticoagulate as long as catheter is in place and for at least 3 months after catheter removal

For Diagnosis and Treatment of Heparin-Induced Thrombocytopenia (HIT), See (VTE-G)

[1] Agent selection based on: Renal failure (C_{cr} < 30mL/min), inpatient/outpatient, FDA approval, cost, ease of administration, monitoring, and ability to reverse anticoagulation.

[2] If warfarin is selected for chronic secondary prevention of recurrent VTE, initiate warfarin concomitantly with the parenteral agent used for acute therapy. Discontinue parenteral therapy when the INR is between 2.0-3.0 for two consecutive days and after a minimum overlap of 5 days with the parenteral agent.

[3] Follow institutional standard operating procedures (SOP) for dosing schedules, if no SOP then use the American College of Chest Physicians (ACCP) recommendations. Kearon C, Kahn SR, Agnelli G, Goldhaber S, et al. Antithrombotic Therapy for Venous Thromboembolic Disease: American College of Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133(6)[suppl]:454S-545S. (www.chestjournal.org)

[4] Following initiation of heparin: Hemoglobin, hematocrit, and platelet count every 2-3 days up to at least day 14 and every two weeks thereafter or as clinically indicated.

[5] LMWHs should be used with caution in patients with renal dysfunction. Dose adjustments and Anti-Xa monitoring may be required. Follow package insert for renal dysfunction and body weight based dosing.

[6] Although each of the low molecular weight heparins (LMWH) have been studied in randomized controlled trials in cancer patients, dalteparin's efficacy in this population is supported by the highest quality evidence and it is the only LMWH approved by the FDA for this indication. Lee AYY, Levine MN, Baker RI, Bowden C, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. New Eng J Med 2003;349(2): 146-153.

[7] Tinzaparin should be avoided in patients over 70 years of age with renal insufficiency. Refer to the FDA website for additional information: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Innohep

[8] Fondaparinux is contraindicated in patients with creatinine clearance < 30 mls/minute and should be used with caution in patients with moderate renal insufficiency (creatinine clearance 30-50 mls/minute), weight < 50 kg or age > 75 yrs.

[9] INR should be checked at 1-2 week intervals in clinically stable patients after the dose has been established.

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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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Venous Thromboembolic Disease

CLINICAL SCENARIOS WARRANTING CONSIDERATION OF FILTER PLACEMENT

- Contraindication to anticoagulation[1]
- Failure of anticoagulation[2]
  - Pulmonary embolism while on adequate anticoagulation for DVT
  - New pulmonary embolism while on adequate anticoagulation for PE
- Patient non-compliance with prescribed anticoagulation
- Baseline cardiac or pulmonary dysfunction severe enough to make any new or recurrent PE life threatening
- Patient with documented multiple PE and chronic pulmonary hypertension

[1] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
[2] See Anticoagulation Failure (VTE-H).

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DIAGNOSIS AND TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Clinical Presentation:

- **Exposure to unfractionated heparin (UFH) or LMWH for 4-14 days or previous exposure within the prior 2 weeks[1]**
- **Unexplained platelet count decrease by > 50% below pretreatment baseline**
- **Necrotic skin lesions at injection sites**
- **Recurrent or progressive thromboembolism on therapeutic doses of UFH or LMWH**

Diagnostic Workup:

- **Exclude other causes of thrombocytopenia (ie, chemotherapy, other drugs, DIC, TTP, antiphospholipid syndrome)**
- **Assess for heparin-associated antibody (ELISA or agglutination assay for platelet factor-4 heparin antibody or serotonin release assay)**
- **Assess for venous and arterial thrombosis to rule out HIT with thrombosis**

[1] Rapid onset HIT (occurs upon exposure to UFH or LMWH for < 2 days) and delayed onset HIT (occurs days to weeks after UFH or LMWH has been stopped) are less common.

Continued on next page

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DIAGNOSIS AND TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)---Continued

Treatment:

- **Immediate Management:**
  - **Discontinue UFH or LMWH and administer a direct thrombin inhibitor (DTI) or fondaparinux**
    - **Argatroban (2 mcg/kg/minute IV infusion, target aPTT 1.5-3 x control) (Dose reduction often required in critically ill and hepatic dysfunction patients)**
    - **Lepirudin (0.1 mg/kg/hour IV infusion, target aPTT 1.5-2 x control) (Dose reduction required in renal insufficiency)[2]**
    - **Bivalirudin (0.15-0.20 mg/kg/hour IV infusion, target aPTT 1.5-2.5 x control)[3]**
    - **Fondaparinux (5 mg [< 50 kg]; 7.5 mg [50-100 kg]; 10 mg [> 100 kg] subcutaneous daily)[4,5]**
  - **Continue treatment:**
    - **If antibody results are positive or presumptively until antibody results are available**
    - **If clinical suspicion of HIT is high or patient requires ongoing anticoagulation**
    - **Initial treatment can be discontinued if antibody results are negative.**
- **Acute Management:**
  - **Start warfarin at maintenance dose when platelet count recovered to >100-150,000/mcL; allow at least 5 days overlap of initial treatment and warfarin; discontinue initial treatment when therapeutic effect of warfarin achieved.**
  - **Argatroban and bivalirudin prolong INR. The duration of this effect is extended in argatroban-treated patients with hepatic dysfunction.**
  - **Platelet transfusions should be avoided unless clinically significant bleeding is present or prior to invasive procedure if already under treatment with a DTI.**
- **Chronic Management:**
  - **Continue warfarin**
    - **Target INR of 2.5 (range 2.0-3.0)**
    - **Complete 1 month of anticoagulation if no thrombosis or other indication to continue (all patients with confirmed HIT require anticoagulation for 1 month because of the high ongoing risk of thrombosis after discontinuing heparin)**
    - **Complete full course of anticoagulation as indicated by thrombotic event**

[2] Refludan package insert (Hoechst Marion Roussel--U.S.), Rev 3/98, Rec 3/98.

[3] Bivalirudin dose reduction is necessary in patients with renal insufficiency or combined renal/hepatic insufficiency.

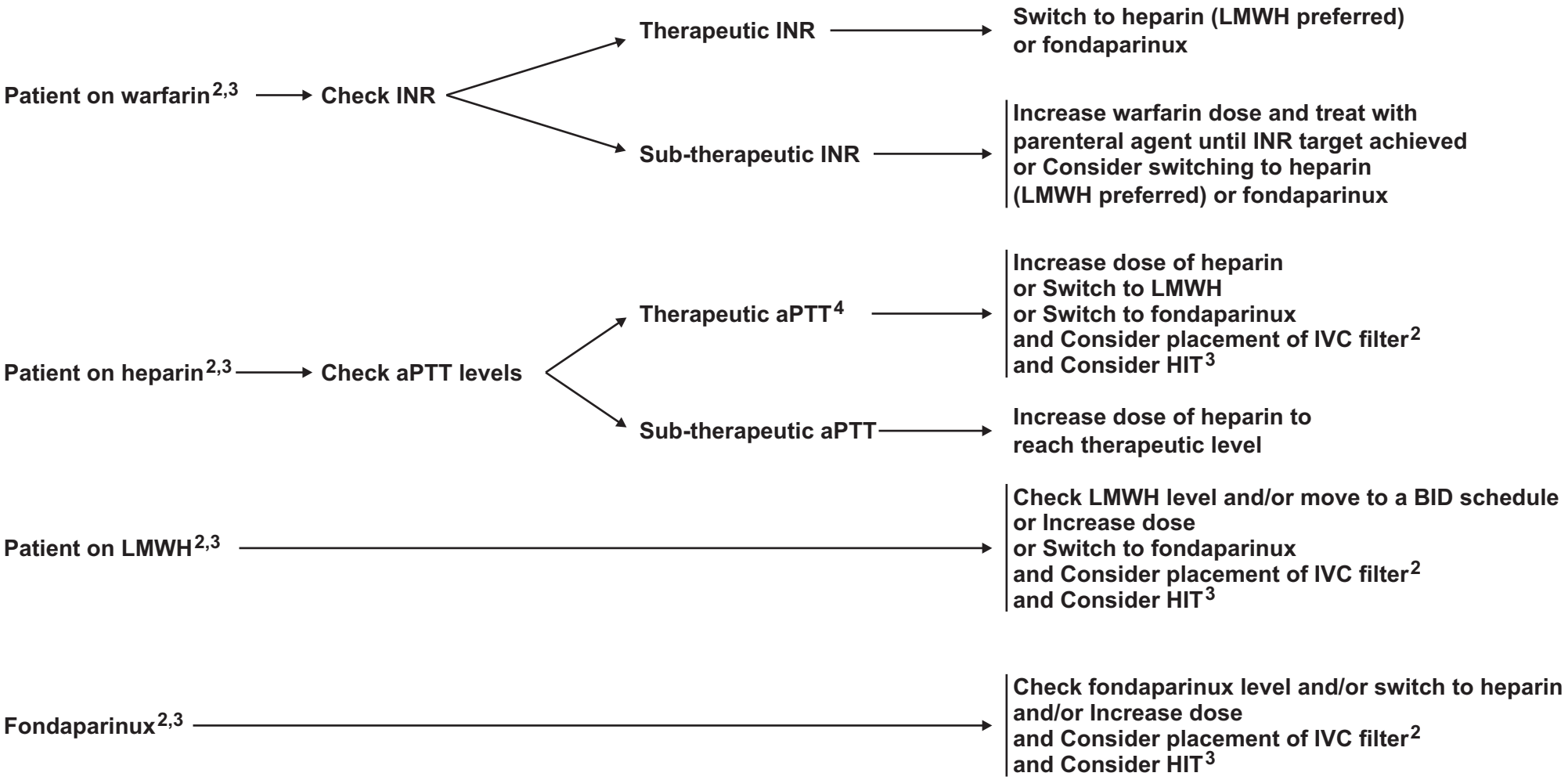
[4] Fondaparinux is contraindicated in patients with creatinine clearance < 30 mls/minute and should be used with caution in patients with moderate renal insufficiency (creatinine clearance 30-50 mls/minute), weight < 50 kg or age > 75 years.

[5] Fondaparinux is not recommended for HIT with thrombosis or in place of a DTI for the immediate management of HIT. Following initial treatment of HIT with a DTI, fondaparinux can be used in selected patients who are ready to be discharged, whose INR is not yet therapeutic on warfarin. The evidence supporting the use of fondaparinux in the immediate management of HIT is weaker than for a DTI.

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

Venous Thromboembolic Disease

THERAPEUTIC ANTICOAGULATION FAILURE[1]



[1] Anticoagulation failure is defined as an extension of DVT or new DVT or PE, while on therapeutic levels of recommended anticoagulation therapy (VTE-D).

[2] If failure of anticoagulation involves a PE or central DVT progression, recommend placement of a filter to prevent recurrent fatal PE, and consider thrombolysis for high risk patients (for pulmonary vascular embarrassment or threatened extremity loss)..

[3] Evaluate for HIT (See VTE-G). If clinical suspicion of HIT is high, see (VTE-G).

[4] Therapeutic aPTT range based on hospital SOP range or 2.0-2.5 x control, if local ranges are unavailable.

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

Manuscript

This manuscript is being updated to correspond with the newly updated algorithm. Last updated 06/26/08

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Venous thromboembolism (VTE) is a common and life threatening condition in cancer patients.[1,2] Results from a recent retrospective study of 66,106 hospitalized adult neutropenic cancer patients showed that 2.74% to 12.10% of these patients, depending on the type of malignancy, experienced VTE during their first hospitalization.[1] The NCCN VTE guidelines 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 (i.e., contraindications to anticoagulation) and the cancer status of the patient.

The definition of VTE includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). In these guidelines, DVT is divided into 4 categories, which differ in terms of associated morbidity, treatment, and long-term effects. These categories include upper extremity; distal lower extremity (e.g., calf); central/proximal (e.g., superior vena caval [SVC], inferior vena caval [IVC], pelvic, iliac, femoral, and popliteal); and central venous catheter (CVC)-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.[3-5] Pathophysiologic explanations of the etiology of VTE in cancer include known hypercoagulability (e.g., procoagulants such as tissue factor from cancer cells), vessel wall damage, and vessel stasis from direct compression.[6-8] The incidence of cancer-associated VTE is further increased by additional risks factors such as thrombophilic mutations, prolonged immobilization, surgical procedures, and chemotherapeutic regimens[9].

The occurrence of VTE has been reported to increase the likelihood of death for cancer patients by 2- to 8-fold.[10-14] For example, gynecologic oncology patients with PE were found to have a 6-fold increase in risk of death at 2 years compared with similar patients without PE.[14] Furthermore, VTE has been reported to be the most common cause of death at 30-day follow-up for 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 several recent 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 recently published multinational IMPROVE registry of hospitalized medically-ill patients in which only 45% of cancer patients received any form of VTE

prophylaxis.[17] 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 occurred in nonsurgical patients.[18]

To address the important problem of VTE in cancer patients, the National Comprehensive Cancer Network (NCCN) initially convened a panel of experts in 2005 and then each year thereafter. The Venous Thromboembolic Disease Panel (an interdisciplinary group of representatives from NCCN member institutions) includes medical and surgical oncologists, hematologists, cardiologists, internists, interventional radiologists, a nurse, and a pharmacist. These guidelines discuss diagnosis, prophylaxis, and treatment of VTE in cancer patients and provide recommendations for patient care based on clinical research and experience in this field.

VTE Risk Assessment in Patients with Cancer

Many of the risk factors for development of VTE are common to patients with cancer,[19] and several VTE risk factors are exclusive to cancer patients, including the presence of malignancy and the administration of certain drugs used to treat cancer. For example, results from 2 population-based case-control studies showed that the presence of cancer increased the risk of VTE by 4- and 7-fold.[20,21] An increased risk of VTE in patients with cancer has also been supported by the results of other studies.[22,23] Furthermore, researchers have reported cancer as the cause of approximately 20% of the VTE cases seen in the community,[5] and a recent cancer diagnosis and the occurrence of advanced malignancies and distant metastases also increase VTE risk.[2,21] For example, Blom et al.[21] reported an adjusted odds ratio of 19.8 when the VTE risk in solid tumor cancer patients with and without distant metastases was compared.

Several studies have evaluated the association between different types of cancer and the risk of developing a VTE.[1,2,11,21,23,24] For example, pancreatic cancer[1,2,11,23,24] and brain tumors[1,2,11,21,25,26] were associated with a high risk of VTE in a number of the studies. Conversely, breast cancer was associated with a relatively low VTE risk in some studies.[1,27,28] Nevertheless, because of the relatively high prevalence of breast cancer, the occurrence of VTE in a patient with breast cancer is not uncommon.[29] Furthermore, the risk of VTE was shown to increase by 5- to 6-fold when patients with metastatic breast cancer were compared with patients with localized disease.[24] Cumulative 5-year results from the NSABP B-14 and B-20 clinical trials of breast cancer patients with estrogen receptor-positive, node-negative cancer showed that the risk of VTE was higher in patients receiving tamoxifen therapy compared with patients receiving placebo; VTE risk was increased further when patients received tamoxifen plus chemotherapy.[29-31]

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

The association of cytotoxic chemotherapy with the development of VTE in cancer patients has been shown in several studies.[32] For example, in one population-based case-control study, odds ratios of 6.53 and 4.05 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.[20] In another retrospective study, the annual incidence of VTE was 10.9% in patients with colorectal cancer treated with chemotherapeutic regimens.[9] Increased VTE risk was shown to be

associated with the use of exogenous estrogen compounds, such as selective estrogen receptor modulators (e.g. tamoxifen, raloxifene), for the prevention and treatment of certain estrogen-receptor positive cancers.[31, 33-35] 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.[36] Use of estrogenic compounds such as hormone replacement therapy[37,38] or oral contraceptive agents[39] has also been associated with increased risk of developing VTE. Evidence has been presented to support the association of certain anti-angiogenic therapies (e.g., thalidomide in combination with doxorubicin and/or dexamethasone, and lenalidomide in combination with dexamethasone) with an increased incidence of VTE when used in the treatment of multiple myeloma.[40-45] Other agents used in supportive cancer care (e.g., hematologic growth factors) have also been associated with the development of VTE.[46,47] Concomitant use of other therapies associated with the development of VTE may further increase VTE risk.[41]

A number of other VTE risk factors, although not exclusive to cancer patients, are commonly found in this population. These include recent surgery, hospitalization, and prolonged immobilization. For example, Heit[20] reported odds ratios of 21.72 and 7.98 for the development of VTE in cancer patients hospitalized or confined to a nursing home with and without recent surgery, respectively, compared with non-institutionalized patients who had not recently undergone surgery. In addition, a history of prior VTE was identified as an independent risk factor for developing a future VTE.[15,22,48,49] 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.[50] More advanced age, a common characteristic of many cancer patients, was also shown to be associated with an increased risk of VTE.[1,15]

Results from numerous studies have identified the presence of a CVC as a risk factor for development of an upper-extremity DVT (UEDVT),[20,51-54] although discrepancies exist concerning the incidence of CVC-related DVT.[54,55] The association between catheter placement and the development of DVT may be the result of venous stasis and vessel injury after insertion of the CVC[54, 56] or infections occurring as a result of catheter placement.[56,57] Possible reasons for the reported discrepancies in the incidence of CVC-related DVT may include recent improvements in catheter materials and design and the different methods of diagnosing catheter-related DVT used in some of the studies (i.e., clinical, which are symptomatic, versus radiologic, which could be symptomatic or asymptomatic, diagnoses).[54,55]

Not surprisingly, VTE risk was shown to increase with the number of VTE risk factors.[49] A number of VTE risk assessment scoring systems are in existence in which individual VTE risk factors are assigned weighted scores based on the level of VTE risk associated with that factor.[58-60] As none of these scoring systems have been validated for risk assessment of cancer patients, a representative scoring system is not currently included in this version of the guidelines; however, these scoring systems provide support for the use of thromboprophylaxis in all adult inpatients with cancer without contraindications to such therapy. Recently, Khorana et al. have published a risk assessment model to estimate the risk of VTE in outpatients with cancer receiving chemotherapy.[61] If validated in further studies this model could be used to help identify patients in whom primary outpatient VTE prophylaxis should be used during their course of chemotherapy. Randomized clinical trials testing this concept are warranted.

Diagnosis and Evaluation of VTE in Cancer Patients

Diagnosis and Evaluation of DVT

Classic clinical symptoms (e.g., pain, unilateral edema and heaviness in the extremity distal to the site of the venous thrombosis, or edema in

the supraclavicular space) are not present in all cases of acute DVT. Diagnosis of DVT in adults with cancer is facilitated by an increased level of clinical suspicion on presentation of any clinically overt signs/symptoms of acute DVT.

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 composed a minority of the subjects in these studies.[62,63] Therefore, it is 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 (2.0% versus 0.5%, NS due to wide confidence intervals). In addition, the number of false positive D-dimer assays was 3- fold higher in cancer patients compared with non-cancer patients.[64] Further investigation/validation of D-dimer testing and clinical prediction rules are warranted before these strategies are incorporated into the diagnostic evaluation of VTE in cancer patients.

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,[65] although assessment of venous compressibility is considered to be more definitive.[52,66,67] Other advantageous characteristics of ultrasonography include accuracy for diagnosing symptomatic DVT in femoral and popliteal veins; noninvasive methodology; no need for intravenous contrast agents; ability to be performed at the bedside; and lower cost.[65] It has been reported that 2 normal ultrasound examinations obtained 1 week apart exclude progressive lower-extremity DVT,[67] although these types of studies have not been performed in populations with cancer. Disadvantages of ultrasonography include difficulties associated with imaging some of the more central veins, such as large pelvic veins, proximal subclavian vein, the IVC, and the SVC[68, 69]; a lower sensitivity for diagnosing distal lower-extremity DVT and asymptomatic DVT[66]; limitations associated with bandages, casts, or pain; and results that are more operator-dependent.[70]

In cases of negative or indeterminate ultrasound results and a continued high clinical suspicion of DVT, other imaging modalities (listed in order of preference) are recommended. 1) Contrast-enhanced computed tomography (CT) (i.e. indirect CT venography) is reportedly as accurate as ultrasonography in diagnosing femoro-popliteal DVT and provides accurate imaging of the large pelvic veins and IVC.[71,72] However, this method requires relatively high concentrations of contrast agent. 2) Magnetic resonance imaging (MRI; MR venography) provides a sensitive and specific evaluation of the pelvic veins and vena cava without the need for nephrotoxic contrast agents.[73,74] Drawbacks to this method include higher cost, longer imaging times and limited availability in some practice setting.[73] 3) Standard invasive venography, once considered the gold standard for DVT diagnosis, has largely been replaced by less invasive methods.[73]

Few studies of UEDVT have been performed.[52,55,75-78] Although UEDVT is frequently related to the presence of a CVC [52,53,76,77] and associated with catheter malfunction,[55] 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.[52] However, in one study, only 50% of isolated flow abnormalities in the upper extremity were related to the presence of DVT.[75] A CT venogram may provide a more accurate assessment in cases of isolated flow abnormalities associated with an upper extremity. Invasive venography

for the detection of UEDVT should be performed through a peripheral vessel in the extremity, although vein access may be limited by edema.[76]

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

The effectiveness of anticoagulation therapy in patients with established DVT should also 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 symptomatic evidence.

Diagnosis and Evaluation of Superficial Thrombophlebitis

Diagnosis of superficial thrombophlebitis is made primarily on the basis of clinical symptoms (e.g. tenderness, erythema; possible indurated cord associated with superficial vein) and a negative ultrasound finding for DVT. Progression of symptoms should be accompanied by follow-up imaging evaluation. Patients with clots involving the saphenofemoral junction of the greater saphenous vein and the common femoral vein (within 2 centimeter of the junction) should be treated for DVT given the risk of progression into the deep venous system and embolization. Peripheral catheter-related thrombosis is excluded from the definition of superficial thrombophlebitis in these guidelines.

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 (DIC), non-bacterial thrombotic (verrucous) endocarditis, and arterial emboli.[79,80]

Diagnosis and Evaluation of PE

Diagnosis of PE in adults with cancer is facilitated by an increased level of clinical suspicion on presentation of any clinically-overt signs or symptoms of acute PE. Classic clinical signs and/or symptoms (e.g., current or recent history of DVT, unexplained shortness of breath, chest pain, tachycardia, apprehension, tachypnea, syncope, and oxygen desaturation) are not characteristic of all cases of acute PE.

D-dimer testing is not recommended for the diagnosis of PE in cancer patients (see discussion above). 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.[81] They should undergo additional workup and imaging (eg, CT angiography - CTA) to evaluate for PE.

Neither a chest radiograph nor an EKG of 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 (V-Q) lung scan.[82] 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,[83] and inverted T waves in precordial leads may be evident in cases of massive PE.[84]

The NCCN panel recommends CTA, which allows for indirect evaluation of pulmonary vessels, as the preferred imaging method for initial diagnosis of PE. Advantages of this method include accurate imaging of mediastinal and parenchymal structures; accurate visualization of emboli in many regions of the pulmonary vasculature; ability to be performed immediately before indirect CT venography performed to detect DVT[71,85] (since the most common cause of PE is DVT in lower extremities or pelvis[86]); and ability to detect signs of RV enlargement, which can be used in stratifying the patient's risk for adverse clinical outcomes.[87] Disadvantages of CTA include associated radiation exposure and the need for large amounts of contrast agent, particularly when CTA is followed by indirect CT venography.[71]

Alternative imaging modalities for the diagnosis for PE include 1) V-Q lung scan and 2) conventional pulmonary angiography. A V-Q scan is associated with less radiation exposure than CTA, is useful for pregnant patients or patients with renal insufficiency or contrast allergies, and is less invasive than conventional pulmonary angiography. A normal V-Q scan result essentially excludes PE.[71] In a recent noninferiority study, 1417 patients determined to have a high risk of PE according to the Wells criteria were randomized to undergo CTA or V-Q scanning. The results demonstrated that CTA was not inferior to V-Q in ruling out PE. However, significantly more patients were diagnosed with PE using CTA imaging (19.2% vs. 14.2%, 95% CI, 1.1%-8.9%).[88] Elderly patients are more likely than younger patients to be diagnosed with an intermediate probability V-Q scan result.[89] Both intermediate and low-probability V-Q scan results lack diagnostic utility and should be considered indeterminate. Further diagnostic testing should be performed if indicated clinically. In the face of clinical pulmonary embolus, a high-probability V-Q scan does not warrant further documentation before initiating treatment. Invasive conventional pulmonary angiography (direct pulmonary angiography), considered at one time to be the gold standard for diagnosing PE, is infrequently used today. Rarely, this method is combined with clot extraction or thrombolytic therapy. These measures should be planned before and executed simultaneously with conventional pulmonary angiography.

The panel recommends that all cancer patients with suspected PE undergo additional testing on hospital admission and be risk-stratified according to outcome. This evaluation is imperative to prevent early discharge of high-risk patients. Additional tests include measurement of serum cardiac troponin, which can detect myocardial cell damage resulting from increased pulmonary vascular resistance and is associated with RV function,[90,91,92] and either echocardiography (transthoracic or transesophageal)[93-95] or a chest CT scan to provide a more direct assessment of RV function.[87] The latter evaluation can be done at PE diagnosis if CTA is used. Patients at higher risk for adverse clinical outcomes are more likely to have elevated troponin levels and evidence of right heart enlargement or dysfunction. Risk stratification systems using biomarkers and imaging with echocardiography or CT[91,96,97] or with other parameters, such as systolic blood pressure and heart failure,[98] have been developed for predicting an adverse outcome in patients with acute PE, although these specific systems are not currently included in the NCCN guidelines.

If imaging to detect the source of the PE is not previously documented, the panel recommends it. In cases in which V-Q scan results are indeterminate for PE, patients should be evaluated for possible DVT, preferably using ultrasound, as described previously. If ultrasound results are negative and clinical suspicion of PE is low, PE is unlikely.

Risks and Relative Contraindications Associated with Anticoagulation in Cancer Patients

Relative Contraindications to Anticoagulation

Contraindications to anticoagulation, possibly of a temporal nature, that place patients at an increased risk of bleeding may include clinically

significant active or chronic bleeding, recent surgery with a high associated bleeding risk, thrombocytopenia or platelet dysfunction, and abnormalities associated with clotting factors, such as those associated with a prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT). The panel recommends frequent re-evaluation of these contraindications and the risks and benefits of anticoagulation therapy for any cancer patients considered to be at increased risk for bleeding to facilitate the implementation of such therapy if and when it becomes clinically prudent.

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 low molecular weight heparins (LMWHs) and fondaparinux include boxed warnings specifying that the risk of 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.[99-102] Unfractionated heparin (UFH) should be also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture.[103] 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 relative contraindication to anticoagulation therapy in patients with a lupus inhibitor or lupus anticoagulant (e.g., 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 of venous and arterial thromboembolism as well as adverse pregnancy outcomes. Any patient who has experienced a thrombotic event and fulfilled diagnostic criteria for antiphospholipid syndrome should be considered for indefinite anticoagulation therapy.[104]

Risks Associated with Anticoagulation Therapy

The use of anticoagulant agents in cancer patients is complicated by the fact that these patients have higher risks of both recurrent VTE and bleeding.[50,105,106] In one prospective follow-up study of patients undergoing anticoagulation therapy for VTE, the 12-month cumulative incidences of major bleeding were 12.4% and 4.9% in patients with and without cancer, respectively (hazard ratio, 2.2; 95% CI, 1.2–4.1).[50] In this study, one third of all cases of major bleeding occurred in the 5 to 10 days of initial heparinization, and the risk of bleeding increased with the extent of cancer. In contrast to patients without cancer, cancer patients remain at increased risk for bleeding during vitamin K antagonist therapy regardless of International Normalized Ratio (INR) level.[105,106] These findings suggest that factors other than the intensity of anticoagulation (e.g., thrombocytopenia, organ or vascular invasion by tumors, etc.) 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 major bleeding.[107-109] Other risks associated with chronic use of anticoagulant agents include osteoporosis and heparin-induced thrombocytopenia (HIT) for patients receiving heparins, and drug and food interactions for patients receiving oral anticoagulants. For example, decreases in bone mineral density of 1.8% and 2.6% and 3.1% and 4.8%, at 1 and 2 years of follow-up, were seen in patients who underwent chronic anticoagulant therapy for 3 to 24 months with an oral anticoagulant or enoxaparin, respectively.[110]

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.[111,112] Furthermore, certain chemotherapeutic agents such as the fluoropyrimidines (e.g., 5-fluorouracil and capecitabine) are known to increase the INR in patients undergoing anticoagulation with warfarin,[113,114] and drug interactions between warfarin and certain selective estrogen receptor modulators (e.g., tamoxifen and raloxifene) have also been reported.[115] Dietary intake of vitamin K and certain dietary supplements can also influence the effects of warfarin.[116, 117] Finally, acetaminophen, found in many medications, can increase the therapeutic effects of warfarin when taken in daily doses exceeding 2 grams.[118]

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.[119,120] 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.[78,120,121] Clinical evidence for the safety and efficacy of anticoagulation therapy in cancer patients is described later. It is the directive of the NCCN that all adult, hospitalized patients with cancer receive anticoagulation therapy in the absence of contraindications (category 1).

Anticoagulants

VTE-C, VTE-D, and VTE-G list the anticoagulation agents used in the prophylaxis and/or treatment of VTE that are included in the guidelines and describe the application of these therapies according to guideline recommendations. Food and Drug Administration (FDA) indications as well as NCCN recommendations for use of each of these therapies are listed in the NCCN Venous Thromboembolic Disease Drugs & Biologics Compendium (for the latest version of the compendium, please visit www.nccn.org). The panel recommends that agent selection be based on criteria such as presence of renal failure; FDA approval; cost; ease of administration; need for monitoring of response; and ability to reverse anticoagulation. Suggested dosing schedules included on VTE-C, VTE-D, and VTE-G were established according to 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.[78,121] (http://www.chestjournal.org/cgi/content/full/126/3_suppl/338S; http://www.chestjournal.org/cgi/reprint/126/3_suppl/401S).

Low-molecular weight heparins

LMWHs such as dalteparin, enoxaparin, and tinzaparin offer advantages of outpatient treatment and eliminate the need to monitor anticoagulant response for most patients. Although the 3 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 3 agents differ pharmacologically with respect to mean molecular weight, half-life, and ability to inhibit thrombin and factor Xa.[122] Recent results from a randomized clinical study comparing tinzaparin to dalteparin in the treatment of DVT and PE in 505 patients including 113 with active cancer support the suggestions that these 2 drugs are equivalent in efficacy (recurrence of VTE) and safety,[123] although results of studies in patients with renal insufficiency suggest that not all LMWHs behave

identically in this population of patients (see below). Enoxaparin[101] is approved by the FDA for both prophylaxis and immediate treatment of VTE; tinzaparin[100] is currently approved only for immediate VTE treatment; and dalteparin[102] is approved for VTE prophylaxis, and also for extended treatment of symptomatic VTE in patients with cancer.

NCCN recommended dosing regimens for dalteparin in immediate VTE treatment and tinzaparin in VTE prophylaxis are based on results of clinical studies and panel consensus.[108,123-127] 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.[108] In addition, the European Society for Medical Oncology (ESMO) clinical recommendations for management of VTE in cancer patients specifies using 75%-80% of the initial dose of LMWH for extended anticoagulation therapy.[128]

Only limited evidence exists concerning the safety and efficacy of LMWHs in special populations such as patients with renal insufficiency, obese patients (patients with a body mass index > 30 kg/m^2), patients weighing < 50 kg, elderly patients (≥ 70 years), and patients with cancer.[129-131] Of the 3 LMWHs, specific dosing recommendations for patients with severe renal insufficiency (creatinine clearance [C_{cr}] < 30 mL/min) are available for enoxaparin only.[101,132] Manufacturer recommendations specify 30 mg enoxaparin subcutaneous daily for VTE prophylaxis and 1mg/kg subcutaneous every 24 hours for VTE treatment for patients with C_{cr} less than 30 mL/min. These recommendations are supported by results of a meta-analysis showing enoxaparin to be associated with a 2-3 fold increased risk of bleeding when administered in standard, unadjusted therapeutic doses to patients with severe renal insufficiency compared with patients without severe renal insufficiency.[133] In another study, renal clearance of enoxaparin was shown to be reduced by 31% and 44% in patients with moderate and severe renal impairment, respectively, leading the authors to suggest dosage reductions for patients with C_{cr} values less than 50 mL/min.[134] Furthermore, some evidence supports downward dose adjustments of LMWH in the management of patients with C_{cr} of 30 to 60 mL/min.[135] Only very limited data are available with respect to the safety of dalteparin and tinzaparin in this population, although there is some evidence for the safety of short-term dalteparin therapy in patients with C_{Cr} values down to 16 mL/min.[136] In addition, tinzaparin, unlike enoxaparin, did not accumulate when used as VTE prophylaxis for 8 days in elderly patients with a mean creatinine clearance of 35 mL/min,[137] or in elderly patients with renal insufficiency receiving therapeutic doses of tinzaparin for a mean duration of treatment of either 10 days[138] or 19+/- 10 days.[139]

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.[101] The panel also recognizes current evidence suggesting caution should also 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 body mass index of 40 kg/m^2 or greater.[140] 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 weighting less than 50 kg,[100-102] 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, fondaparinux or a direct thrombin inhibitor (DTI) is a better alternative option. Later sections summarize the clinical evidence for the safety and efficacy of LMWHs in cancer patients.

Specific Inhibitor of Factor Xa

Fondaparinux is the only specific factor Xa inhibitor approved by the FDA for the prophylaxis and treatment of VTE.[99] 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 lack of cross reactivity with the antibody associated with HIT.[99,141-144] However, the use of fondaparinux in patient populations with renal insufficiency, obesity,[131] or HIT[142] has not been well defined, 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.[145] Pharmacologic characteristics of fondaparinux include renal elimination and a very long half-life of 17 to 21 hours.[99] 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. It should be used with caution in elderly patients[145] and individuals with moderate renal insufficiency (C_{cr} < 50 mL/min).[99] 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 < 50kg, patients with renal dysfunction (creatinine clearance 30-45 ml/min), and elderly patients.

Unfractionated Heparin

UFH for use in the prophylaxis of VTE is administered subcutaneously (low-dose heparin), but intravenous heparin is indicated to treat VTE.[146] Low-dose UFH (5000 units) administered 3 times a 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[147] and is the regimen recommended by the panel for the prophylaxis of VTE in cancer patients. Initial dosing of UFH in the treatment of VTE is weight based, with a recommended regimen of 80 units/kg load followed by 18 U/kg per hour infusion.[130] 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,[148] but further investigation is needed before this regimen can be routinely used in cancer patients. Patients receiving intravenous UFH must initially be hospitalized and monitored for anticoagulant response. The panel recommends UFH as the agent of choice in patients with C_{cr} less than 30 mL/min, because the liver is a main site of heparin biotransformation.[103,143,149] 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, fondaparinux or a DTI is a better alternative option.

Warfarin

Warfarin is an option for cancer patients with VTE. Initially, when warfarin is the choice for chronic anticoagulation, it should be administered concomitantly with UFH, LMWH, or fondaparinux, except when treating HIT where warfarin administration, in most situations, is initially overlapped with administration of a DTI. Daily and then frequent (at least every 1-2 weeks) monitoring of the INR is required. Warfarin can be safely administered to patients with renal insufficiency, although response to warfarin may be potentiated in patients with hepatic insufficiency.[150]

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) are discussed in a later section.

Mechanical Devices

Sequential compression devices

One of the main advantages of pneumatic venous compression devices (VCDs) 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.[121] Graduated compression stockings can be used in conjunction with a VCD as a method of mechanical prophylaxis.

Vena Cava Filters

Placement of a vena cava filter[151,152] has the main advantage of preventing PE in patients at high risk of VTE and those with VTE who have contraindications to anticoagulant therapy.[153-158] However, placement of an IVC filter does not prevent DVT and has been associated with an increased risk of recurrent DVT in some studies.[157,159,160] Only one randomized, controlled trial has been conducted on the efficacy and safety of IVC filters compared with anticoagulant therapy.[157,160]

There are retrievable and permanent IVC filters. However, the time period for recovery of a retrievable filter is limited.[161,162] Results from a recent 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 60.8% of those attempts were successful.[163] No significant differences in protection or complication rates were observed with the 2 types of filters. Since every retrievable filter has the potential to become a permanent filter, and all such filters are also FDA approved as permanent devices,[162] most patients with a contraindication to placement of a permanent IVC filter are not likely to be candidates for a retrievable filter. The panel considers placement of a permanent filter to be preferable if the patient requires an IVC filter for longer than 1 month or longer than manufacturer's recommendation, or if their relative risk of bleeding exceeds these time periods.

VTE Prophylaxis

Mechanical Prophylaxis

Mechanical prophylaxis with VCDs should be considered for all hospitalized patients with a diagnosis of cancer in the absence of contraindications to mechanical prophylaxis (e.g., arterial insufficiency, open wound, etc.), regardless of perceived risk of bleeding. VCDs should be used concomitantly with anticoagulation therapy in the absence of high bleeding risk or without anticoagulation therapy in patients with one or more contraindications to such therapy. Steps should be taken to ensure the continuous application of VCDs.

VCDs have been less well studied than the use of anticoagulation therapy in VTE prevention.[121] Most of the data on the effectiveness of mechanical prophylaxis have come from surgical populations. For example, in a study comparing 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 intermittent pneumatic calf compression, no difference was seen between the 2 modalities.[164] A retrospective evaluation of high-risk colorectal surgery patients who had received mechanical prophylaxis without anticoagulant therapy indicated that VCDs were effective in preventing postoperative VTE.[165] However, results from a recent 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 showed 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%).[166] Therefore, VCDs should only be used alone for VTE prophylaxis in patients in whom anticoagulant prophylaxis is contraindicated.

Graduated compression stockings have been demonstrated to significantly reduce VTE in comparison to no prophylaxis and provide even greater protection when combined with other preventive therapies.[167] 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 recent randomized controlled trial in hip surgery patients found that GCS did not provide significant additive protection against VTE in patients receiving fondaparinux 2.5 mg daily for 5-9 days, suggesting that GCS may not have significant clinical benefits in patients able to receive more potent forms of VTE prophylaxis.[168] Although further investigation of this finding is warranted, GCS should not be relied upon as the sole form of VTE prophylaxis in cancer patients but should be combined with a VCD at a minimum.

Prophylactic Anticoagulation Therapy

Inpatient Prophylactic Therapy

The panel recommends prophylactic anticoagulation therapy for all inpatients with a diagnosis of active cancer (or for whom clinical suspicion of cancer exists) who do not have a 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 on VTE-C. Anticoagulation therapy should be administered throughout the duration of hospitalization. Adult inpatients with cancer should undergo the following tests prior to the initiation of thromboprophylaxis: comprehensive medical history and physical examination; complete blood count (CBC) with platelet count; prothrombin time (PT); activated partial thromboplastin time (aPTT); and serum creatinine.

Studies comparing different anticoagulant regimens for the prevention of VTE in cancer patients have not clearly identified a particular regimen with superior efficacy. For example, no difference in VTE and bleeding rates were seen for cancer patients receiving perioperative enoxaparin (40 mg) once daily or low-dose UFH 3 times a day to prevent VTE after major elective abdominal or pelvic surgery.[169] 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.[170] However, results from a recent 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.[171]

For prevention of VTE associated with a CVC, no difference in CVC-related VTE rates was seen in double-blind, placebo-controlled, randomized studies of cancer patients undergoing prophylaxis with enoxaparin for 6 weeks [172,173] or dalteparin for 16 weeks.[174] Therefore, the panel does not recommend VTE prophylaxis for cancer patients with a CVC.

Outpatient Prophylactic Therapy

Cancer patients are known to remain at risk for VTE after discharge from the hospital. The risk of VTE is sufficiently high in some surgical and medical oncology patients that VTE prophylaxis should be considered in the outpatient setting. Cancer patients at high risk for VTE include patients undergoing abdominal or pelvic surgery.[166] Additional VTE risk factors for surgical oncology patients with a previous episode of VTE include anesthesia times longer than 2 hours, advanced stage disease, bed rest ≥ 4 days and patients age 60 years or older.[15] Extended prophylaxis out to 4 weeks post-surgery was associated with a greater than 50% reduction in venographic VTE in

patients undergoing major abdominal surgery.[175,176] Since thromboembolic post-operative complications greatly exceeded hemorrhagic complications as a cause of death in the @RISTOS observational cohort study of cancer surgery patients,[15] extended (up to 4 weeks) VTE prophylaxis is recommended for high-risk cancer surgery patients.

Although there are no data to support extended outpatient prophylaxis of medical oncology patients, patients receiving highly-thrombogenic chemotherapy should also be considered for prophylactic anticoagulation. Anti-angiogenic agents such as thalidomide or lenalidomide have been associated with VTE rates of 10% -20% in patients with multiple myeloma when combined with dexamethasone or doxorubicin-containing chemotherapy regimens.[43-45] Recommended anticoagulant options for VTE prophylaxis of cancer patients following discharge from the hospital are listed on VTE-C.

VTE Treatment

Upon diagnosis of VTE, the panel recommends beginning immediate treatment (5-7 day duration) with either UFH (IV), LMWH, or in some cases, fondaparinux in cancer patients without contraindications to anticoagulation. 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 to it use in the acute period exist. In the event that warfarin will be used for chronic therapy, there should be a short-term, transition phase of at least 5-7 days during which the acute parenteral anticoagulant (e.g., UFH, LMWH or fondaparinux) is overlapped with warfarin until an INR of 2 or more is achieved. Cancer patients with a DVT should be treated for a minimum treatment time of at least 3-6 months while patients with PE should be treated for at least 6-12 months with either a LMWH or warfarin**.** LMWH as monotherapy (without warfarin) is recommended for chronic treatment of proximal DVT or PE, and 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 in this decision. 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 of longer than 6 months, decisions relating to whether 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 considered for patients with lower-extremity DVT characterized as progressive, central/proximal DVT, or PE who have contraindications to anticoagulation, PE while on adequate anticoagulation for DVT, or new PE while on adequate anticoagulation for PE. Placement of an IVC filter should also be considered for patients who are non-adherent with prescribed anticoagulation, those with baseline cardiac or pulmonary dysfunction severe enough to make any new or recurrent PE life threatening, and those with documented multiple PE and chronic pulmonary hypertension. The decision of whether to place a permanent or retrievable IVC filter should be determined by the anticipated duration of need. Patients with long-term contraindications to anticoagulation should have permanent filters placed whereas patients with temporary requirements for IVC filtration should have a retrievable filter placed. 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.

Patients in whom VTE has been diagnosed or for whom there is a clinical suspicion of DVT or PE should undergo a comprehensive medical history and physical examination; complete blood count (CBC)

with platelet count; prothrombin time (PT); activated partial thromboplastin time (aPTT); and serum creatinine prior to initiation of (empiric) treatment with anticoagulation.

Immediate VTE Treatment

Results from a meta-analysis of randomized, controlled clinical trials comparing LMWH and UFH in the immediate treatment of VTE (e.g., initial treatment for a minimum of 5-10 days) showed no statistically significant difference in efficacy of these 2 agents for preventing recurrent VTE.[177] A randomized, open-label trial of the use of fondaparinux versus UFH administered to hemodynamically stable patients with PE for at least 5 days indicated that both agents were equally effective for preventing recurrent VTE.[178] In both treatment arms, warfarin therapy was started within 72 hours of treatment initiation and initial therapy with either fondaparinux or UFH was stopped when an INR greater than 2.0 was attained. Furthermore, the incidences of adverse events associated with the 2 therapies were similar. However, only approximately 16% of patients enrolled in this study were identified as having either a history of cancer or active cancer. The current evidence does not support identifying one of these agents as the most efficacious and/or safest choice in patients with cancer, although fully reversible UFH may be preferable in patients with a higher risk of bleeding[143].

Chronic VTE Treatment

Several studies comparing the efficacy and safety of LMWH and oral vitamin K antagonists (i.e., warfarin) in the chronic treatment of VTE in patients with cancer have been performed. In one randomized, open-label trial (The 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 the treatment of 146 cancer patients with VTE.[107] The primary endpoint of this study was a combined outcome event including major bleeding and recurrent VTE. In the groups receiving chronic enoxaparin and warfarin, 10.5% and 21.1% of patients, respectively, experienced either major bleeding or recurrent VTE (P = 0.09) within 3 months. No significant differences in bleeding or recurrent VTE were observed when patients with active cancer and VTE were randomly assigned to receive either 6 months of enoxaparin (either 1.5 mg/kg or 1 mg/kg q24h) or immediate enoxaparin therapy followed by warfarin to complete 6 months of therapy (ONCENOX trial).[179]

The randomized, multicenter LITE study evaluating the use of chronic (84 days) tinzaparin versus immediate (5 days) UFH followed by chronic (84 days) warfarin therapy in high-risk patients with proximal-vein VTE reported no significant differences in VTE recurrence rates between the 2 groups overall.[180] However, bleeding complications were significantly higher for the overall group receiving warfarin therapy. A subset analysis of the 200 cancer patients enrolled in the LITE trial showed a significantly increased rate of VTE in the group receiving warfarin therapy at 12 months (16% vs. 7%; P=0.044), whereas bleeding rates in the 2 groups were not significantly different.[109] Finally, the CLOT trial compared the efficacy and safety of immediate (5–7 days) dalteparin followed by chronic (6 months) therapy with an oral coumarin derivative with chronic dalteparin therapy in patients with cancer, the majority of which had metastatic disease, after diagnosis of acute proximal DVT, PE, or both.[108] This study showed probabilities of recurrent VTE at 6 months of 17% and 9% (hazard ratio=0.48; P=0.002) in cancer patients receiving oral anticoagulants and dalteparin, respectively. No significant difference in bleeding or PE rate was seen for the 2 groups. 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, that the efficacy difference was observed for development of recurrent DVT only

(not PE), and uncertainty on whether these results can be extrapolated to LMWHs other than dalteparin. Combining the results of all these studies, a Cochrane review of anticoagulation for the chronic treatment of VTE in patients with cancer found no significant differences in bleeding, thrombocytopenia or survival outcomes with use of LMWH compared with oral vitamin K antagonists.[181] However, the incidence of VTE was significantly lower for patients receiving LMWH (hazard ratio=0.47; 95% CI, 0.32-0.71)

Increased survival rates have been reported for subgroups of cancer patients receiving chronic treatment with dalteparin versus other VTE therapies or placebo.[182,183] 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 suggested that 1-year survival rates were higher for patients receiving dalteparin compared with patients receiving placebo.[183] A posthoc 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 oral VTE therapy.[182] Results of several other randomized studies have also provided evidence of improvement in survival of cancer patients receiving LMWHs.[184,185] In addition, conclusions from a Cochrane review regarding the antineoplastic properties of anticoagulants were 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.[186] Additional evaluations of the putative anti-tumor effects of LMWHs are needed before recommendations pertaining to this issue can be made.

Treatment of Central Venous Catheter (CVC)-Related DVT

The central tenant guiding the treatment of CVC-related DVT is based on the question of whether the catheter is required for continued treatment of the patient. Catheter removal is recommended in the case of CVC-related DVT when the catheter is no longer required or when the catheter is required but relative contraindications to anticoagulation therapy exist. Anticoagulation therapy is recommended while the catheter is in place (in the absence of contraindications) and for 1 to 3 months after catheter removal. If the catheter is required but DVT symptoms persist or a clot continues after anticoagulation therapy is started, the panel recommends that the catheter be removed. Patients with CVC-related DVT and relative contraindications to anticoagulation therapy should be followed for changes in these contraindications as clinically indicated; anticoagulation therapy is recommended after contraindications are resolved.

No randomized, controlled trials have been reported evaluating the effects of particular therapeutic strategies on outcomes of CVC-associated VTE. A recent prospective study of 444 cancer patients with CVC showed an incidence of symptomatic catheter-related DVT of 4.3%.[55] Of 19 patients with catheter-related DVT, 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 DVT revealed that residual symptoms of DVT were present in only 2. A recent pilot study of cancer patients with catheter-related, symptomatic UEDVT demonstrated that anticoagulation with dalteparin followed by warfarin (INR 2-3) was associated with no episodes of recurrent VTE and/or line removal as a consequence of thrombosis/infusion failure. Major bleeding occurred in 3 patients (4%).[187]

Treatment of "Massive" DVT

Opinions diverged within the NCCN VTE guidelines panel regarding treatment of "massive" or limb-threatening DVT in cancer patients. The panel advised consideration of catheter-directed thrombolytic therapy in these patients; however, specific recommendations regarding this condition, as distinct from other types of DVT, are not included in the current version of the VTE guidelines.

Treatment of PE

A high-risk patient with PE is defined as a cancer patient with acute PE and abnormal results on risk-stratifying evaluations (e.g., serum cardiac troponin levels and RV function) performed on hospital admission. This population includes hemodynamically unstable patients with imaging evidence of massive PE and stable patients with submassive PE and evidence of moderate or severe RV enlargement or dysfunction. RV dysfunction may be exacerbated by congestive heart failure (CHF) or chronic obstructive pulmonary disorders (COPD). The added burden of PE in the presence of CHF or COPD provides some justification for considering thrombolytic therapy in patients with acute PE who appear hemodynamically stable but are at increased risk for adverse outcomes.[92, 188]

In patients without relative 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 along with a concomitant evaluation of the patient's risk of bleeding. In addition, an IVC filter may be considered for this patient population.

A meta-analysis of 9 randomized, controlled clinical studies of unselected patients with acute PE did not show thrombolytic therapy to be superior to anticoagulation therapy with intravenous heparin for reducing mortality or PE recurrence, and it was associated with an increased bleeding risk.[189] Another meta-analysis of the same 9 clinical trials indicated that patients receiving thrombolytic therapy were less likely to experience a composite endpoint of recurrence of PE/death than patients receiving IV heparin. However, the difference in PE recurrence rates alone was not statistically significant, and bleeding risk was found to be elevated in the patients receiving thrombolytic therapy.[190] In an updated meta-analysis including 11 randomized trials comparing heparin and thrombolytic therapy in patients with acute PE, no significant differences in reduction of recurrent PE, death, or major bleeding were found.[191] However, a significant decrease in recurrent PE or death was observed for patients receiving thrombolytic therapy in an evaluation of the subset of trials that included patients with hemodynamically unstable PE.[191]

No differences in in-hospital mortality were observed 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 alteplase or heparin plus placebo for 2 hours. Treatment escalation because of clinical instability was significantly increased in the latter group,[192] although the clinical endpoints and other aspects of the design of this trial have been criticized.[193,194] Reports from several recent 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.[195-197] 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 catheter-directed thrombolysis for upper or lower extremity acute symptomatic DVT in patients with or without cancer.[198]

Although the ACCP recommends against the use of thrombolytic therapy or pulmonary embolectomy in most patients with PE, they suggest using thrombolytic therapy in selected patients, such as those with massive PE who are hemodynamically unstable and without a high risk of bleeding. The ACCP suggests use of pulmonary embolectomy for selected patients with critical status who are unable to undergo thrombolytic therapy due to an emergent situation.[78]

Treatment of Superficial Thrombophlebitis

Anti-inflammatory medications, warm compresses, and elevation of the affected limb are recommended for the initial treatment of superficial thrombophlebitis. 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 superficial thrombophlebitis only, not for DVT prophylaxis.

Only a limited number of studies have evaluated the clinical significance of superficial thrombophlebitis, its associated progression to VTE, and the effect of anticoagulant agents on its course.[199,200] In a prospective assessment of 60 consecutive patients with superficial thrombophlebitis of the greater saphenous vein, the combined incidence of DVT and superficial thrombophlebitic 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 therapy.[201] 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 superficial thrombophlebitis showed no significant differences between treatment and placebo groups with respect to progression to DVT.[202] However, all active treatments reduced the combined rate of DVT and superficial thrombophlebitis compared with placebo, although no significant differences were observed between active treatment groups. This possibly indicates that longer treatment durations may be required.

Therefore, prophylactic anticoagulation is not recommended by the panel in cases of uncomplicated, self-limited superficial thrombophlebitis. Anticoagulation therapy (e.g. intravenous UFH or a LMWH for at least 4 weeks) should be considered for patients with superficial thrombophlebitis characterized by symptom progression or patients with involvement of the proximal portion of the greater saphenous vein near its junction with the common femoral vein. Transition to warfarin therapy (INR 2-3) is an option after immediate treatment with a parenteral agent.

VTE Therapies: Response Assessment

Intensive monitoring of the effects of some of the anticoagulant agents on clotting potential is particularly important in patients with cancer.[131] The recommendations on monitoring anticoagulant response included in the NCCN VTE guidelines may be superseded by written SOPs 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 coagulation factors.[130,203] The aPTT measures the overall activity of the intrinsic and common coagulation pathways and is particularly sensitive to agents that inhibit thrombin.[130,204] Therefore, the efficacy and safety of UFH in the treatment of VTE is most commonly evaluated by monitoring the aPTT

and depends on the establishment of an therapeutic aPTT range.[130,146,205] The aPTT therapeutic range should be established by each institution using regular calibration of an aPTT therapeutic range against unfractionated heparin 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.[130,205,206] Such testing should be performed in the clinical laboratories at that 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 2.0 to 2.9 times the control value (i.e., 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.[203]

LMWHs and Factor Xa Antagonist (Fondaparinux)

LMWHs act by potentiating the inhibitory activity of antithrombin against factor Xa and to a lesser extent, thrombin.[130] Fondaparinux is a synthetic indirect Xa inhibitor that also functions through potentiation of antithrombin inhibition.[141] Measurement of factor Xa inhibition, not the aPTT, is necessary to evaluate the anticoagulant effect of LMWH or fondaparinux, because thrombin inhibition associated with LMWH or fondaparinux is weak or absent, respectively.[99,130] 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.[130,143] In general, the panel recommends limiting the use of LMWHs and fondaparinux in patients with renal insufficiency and those at extremes of body weight (as described previously), 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 (DTI)

Lepirudin, argatroban, and bivalirudin are direct inhibitors of thrombin. 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.[203] Target aPTT ranges of 1.5 to 2.0 times control, 1.5 to 3.0 times control and 1.5 to 2.5 times control are recommended when using lepirudin, argatroban, and bivalirudin, respectively. The aPTT range of 1.5 to 2.0 times control for lepirudin is lower than specified by the manufacturer. Recent studies have shown that accumulation of this agent may occur in patients with even mild renal impairment, thereby necessitating more frequent aPTT monitoring and a lower target aPTT range.[207,208]

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.[150] 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.[203]. The panel recommends a target INR of 2.5 (range, 2.0–3.0) for VTE treatment; this range is consistent with ACCP recommendations.[78] Initially, the INR should be checked several times a week (daily may be advisable in inpatients) during the transition phase from co-therapy with a parenteral anticoagulant (i.e., UFH or

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.[209] A recent multicenter randomized clinical trial demonstrated that computer assisted dosing of warfarin was superior to dosing directed by experienced providers.[210] 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),[203,211,212] and the duration of this effect is extended in argatroban-treated patients with hepatic dysfunction.[213]

Reversal of Anticoagulant Activity

The anticoagulant effects of UFH are fully reversible with protamine sulfate, and LMWHs are partially reversed by protamine sulfate (60-80%), although this agent must be used with caution because it can cause severe hypotension or anaphylactoid reactions particularly if it is infused too rapidly.[100-103,130] Therefore, protamine should not be infused more rapidly than 5 mg per minute.[214] No available agents act to directly reverse the activities of specific inhibitors of factor Xa or thrombin, although intravenous recombinant human factor VIIa can be administered to help reduce the anticoagulant effects of LMWHs, DTIs, and fondaparinux.[215] In many cases, the effects of warfarin can be reversed through administration of oral vitamin K.[150] Alternatives to more rapidly reverse warfarin-related coagulopathy include intravenous vitamin K, fresh-frozen plasma, and coagulation factor concentrates such as prothrombin complex concentrates or recombinant human factor VIIa. These are used to reverse serious or life-threatening bleeding and in the rapid preparation of patients for urgent/emergent invasive procedures associated with bleeding risk.

Related Issues in VTE Prophylaxis and Treatment

Failure of Anticoagulation Therapy

Anticoagulation failure is defined as extension of DVT or PE, or new DVT or PE, while on recommended anticoagulation therapy.[216] Although there are numerous underlying 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, an option is to increase anticoagulant doses to a therapeutic target.

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 antagonist or subcutaneously administered anticoagulants, and the dosing frequency for patients receiving LMWH.[216] For example, an increased risk of VTE recurrence was reported in one study of cancer patients receiving once-daily enoxaparin in the acute therapy setting.[217] Thus, a twice-daily dosing schedule is an option for patients exhibiting recurrent VTE while receiving once-daily therapy with a 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).

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 (ie, 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 which interact with warfarin.[218,219] An option for patients undergoing warfarin therapy and exhibiting a subtherapeutic INR is a switch to LMWH (preferred), 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.[220] Likewise, heparin resistance (ie, inability to achieve therapeutic aPTT on heparin doses typically used to treat VTE), although rare, can occur as a result of pharmacokinetic or biophysical/physiologic limitations of heparin therapy.[221]

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 Trousseau's syndrome, HIT, cancer-related anatomic causes, such as vascular compression, and acquired and/or familial thrombophilia. [216,221] Diagnostic testing to identify syndromes identified above, when present, is critical to the management of VTE in these patients.[216] In particular, 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 LMWH or fondaparinux or an increase in the dose of UFH. Likewise, patients with recurrent VTE and a therapeutic INR while on warfarin therapy can be switched to heparin (LMWH preferred) or fondaparinux. A switch to LMWH 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 despite therapeutic anticoagulation with UFH, LMWH, or fondaparinux, although filters should be avoided in the setting of HIT or migratory thrombophlebitis (see Trousseau's syndrome) due to the systemic nature of these coagulopathies.[79,80]

Diagnosis and Management of HIT

Specific guideline recommendations regarding HIT are available from the ACCP (http://www.chestjournal.org/cgi/content/full/126/3_suppl/311S).[142] 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.[222] In another study, 2.7% of patients treated with UFH developed HIT.[223] Heparin binding to the platelet alpha-granule protein, platelet factor 4 (PF4), triggers a structural change that elicits antibody production against the neo-epitopes that are uncovered. These antibodies can activate platelets resulting in additional platelet factor 4 release and platelet microparticle formation. Endothelial cells are also activated. The end result is a consumptive thrombocytopenia and profound pro-thrombotic state that triggers symptomatic thromboembolism in a large percentage of cases.[142] It has been estimated that anywhere from 20%-76% of patients with HIT develop thrombotic complications.[130,224] Clinical evidence of HIT can include formation of necrotic lesions at injection sites, arterial thromboembolic complications, and development of VTE.[225,226] Most typically, HIT occurs after 4 to 14 days of exposure to heparin-based products or previous exposure to such agents within a 2 week period. Less common is rapid-onset HIT, occurring less than 2 days after initial administration of the heparin-based product, and delayed-onset HIT, which can occur days or weeks after heparin therapy has been discontinued.

Some evidence indicates that cancer patients are at increased risk of developing HIT and HIT-related VTE,[227] 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.[228] Results of some studies have indicated that the frequency of HIT with LMWH and UFH is similar,[228-230] whereas other studies suggest a lower incidence of HIT in patients receiving LMWH relative to those receiving UFH.[223,231-233] It has been suggested that factors such as anticoagulant dose (ie, 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.[234,235]

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, respectively. Testing for the presence of HIT antibody is warranted after a drop in platelet count by more than 50% or other clinical evidence of HIT. The immediate management of HIT includes discontinuance of heparin-based products and administration of an alternative anticoagulant, typically a DTI (see section below on Anticoagulants for the Treatment of HIT); these measures are recommended before obtaining results of HIT antibody testing if clinical suspicion of HIT is high. Platelets should not be transfused during an episode of HIT unless life-threatening bleeding is present. Warfarin therapy should be initiated on platelet count recovery (e.g., >100,000-150,000/ mcL). After platelet recovery, warfarin should be overlapped with a DTI for at least 5 days and until the target INR is reached for at least 2 days, the platelet count has stabilized, and symptomatic thrombosis is controlled, at which point the DTI is discontinued.[142,208] The panel recommends routine screening ultrasounds for patients with HIT, and warfarin therapy for at least 3 months in patients who experience asymptomatic DVT in association with HIT. In patients with HIT without thrombosis, one month of warfarin therapy (INR 2-3) should be considered.

Anticoagulants for the Treatment of HIT

Both argatroban and lepirudin are direct thrombin inhibitors that have been approved by the FDA for the immediate treatment of HIT.[213,236] Argatroban is primarily metabolized by the liver, and prolonged clearance of this agent has been seen in patients with hepatic insufficiency.[213] Lepirudin is primarily excreted by the kidneys and may accumulate in patients with renal dysfunction, depending on the extent of renal impairment.[236] 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. Recently, Greinacher and Warkentin[208] recommended a lepirudin dosing regimen that is less aggressive than the standard regimen, and results of other studies support use of this regimen.[207,237] Similarly, dosage reductions have also been suggested for bivalirudin,[238] another DTI, when it is used off-label in the treatment of HIT[239] and in patients with HIT and hepatic and/or renal insufficiency or critically ill patients.[240,241]

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. The panel recommends argatroban and lepirudin as the treatments of choice for HIT. Use of argatroban and lepirudin should be avoided in patients with hepatic failure and renal insufficiency, respectively.

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 guidelines.[242] Advantages to the use of fondaparinux in this setting, in addition to subcutaneous

administration, include long half-life, and lack of INR prolongation when administered concomitantly with warfarin. Furthermore, unlike DTIs, aPTT testing is not used to monitor treatment response of fondaparinux, thereby eliminating problems associated with warfarin prolongation of aPTT when overlapped with a DTI. However, rare cases of HIT have recently been reported with use of postoperative prophylactic doses of fondaparinux.[243,244] In one of those cases, the patient had a past history of HIT with thrombosis following prophylaxis with a LMWH, although the other patient had no history of HIT. In light of these recent findings and until in vivo randomized controlled trials comparing fondaparinux with a DTI in the setting of HIT have been conducted, 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 not yet stable on warfarin therapy.[245]

Warfarin therapy in the treatment of HIT should not be initiated until after platelet count recovery because of the potential for skin necrosis and/or venous gangrene, which can occur because warfarin reduces functional protein C levels in the setting of HIT thrombosis.[246] The duration of warfarin therapy is dependent on whether HIT is accompanied by thrombosis. All patients with confirmed HIT require at least 1 month of anticoagulation therapy due to the ongoing risk of thrombosis; length of therapy for those with thrombosis is determined by the particular thrombotic event.

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.[247] 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 of VTE in cancer patients is the first step in preventing the occurrence of VTE and promptly identifying VTE in these patients. The NCCN 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 patients at high-risk of VTE (eg. cancer surgery patients) continue to receive VTE prophylaxis for up to 4 weeks post-operation. Careful evaluation and follow-up 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.

Future Directions

The following research topics have been identified by the panel as areas in need of evaluation in prospective clinical trials:

- VTE prophylaxis in patients with long durations of severe thrombocytopenia (e.g.,acute leukemia and BMT patients): benefits and risks
- VTE prophylaxis in cancer patients with a history of CVC-related DVT at risk of a developing new CVC-related DVT

- Chronic VTE treatment with LMWH: Evaluation of the efficacy and safety of treating VTE in cancer patients with LMWH beyond a 6 month period.
- Safety of LMWH in cancer patients with renal insufficiency.
- IVC filters: Indications for placement of retrievable vs. permanent filters; triggers for filter removal; relative efficacy and morbidity of the 2 filter types.
- Thrombolytic therapy in cancer patients with PE, including patients with submassive PE characterized by RV dysfunction/enlargement, or "massive DVT": effects on morbidity and mortality
- Extended VTE prophylaxis in medical oncology patients: benefits and risks
- Simple VTE risk assessment tools for stratifying cancer patients
- Long-term surveillance of cancer patients at risk of VTE
- Effects of introduction of NCCN VTE Guidelines on management of cancer patients

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