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Venous Thromboembolic Disease

Clinical Practice Guidelines in Oncology

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Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in patients with cancer.[1,2] Results from a retrospective study of 66,106 patients hospitalized with adult neutropenic cancer showed that 2.7% to 12.1% of these patients, depending on the type of malignancy, experienced VTE during their first hospitalization.[1] These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) specifically outline strategies to prevent and treat VTE in adult patients either diagnosed with cancer or for whom cancer is clinically suspected. These NCCN Guidelines are characterized by it-

NCCN Clinical Practice Guidelines in Oncology for Venous Thromboembolic Disease

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, venous thromboembolism, superficial vein thrombosis, cancer, deep venous thrombosis, pulmonary embolism, anticoagulation, heparin, prophylaxis, treatment, low-molecular-weight heparin, warfarin *(JNCCN* 2011;9:714–777)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Venous Thromboembolic Disease

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Venous Thromboembolic Disease panel members can be found on page 777. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

erative 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.

These NCCN Guidelines define VTE broadly to include deep venous thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT), and thrombosis in other vascular territories (e.g., portal vein, mesenteric vein, inferior vena cava [IVC], superior vena cava [SVC], pelvis). DVT management is divided into 5 categories, which differ in terms of associated morbidity, treatment, and long-term effects. These categories include the upper extremity and SVC; the lower extremity, including the IVC, pelvis, iliac, femoral, and popliteal veins; distal lower extremity (e.g., calf); splanchnic vasculature; and central venous access device (CVAD)–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.[3,4] Pathophysiologic explanations of the origin of VTE in cancer include known hypercoagulability (e.g., procoagulants such as tissue factor expressed by cancer cells), vessel wall damage, and vessel stasis from direct compression.[5–7] The incidence of cancer-associated VTE is further increased by the presence of additional risk factors such as acquired or congenital thrombophilia (e.g., antiphospholipid syndrome, factor V Leiden), prolonged immobilization, surgical procedures, and chemotherapeutic regimens[6,8] (see the next section).

Text continues on p. 737

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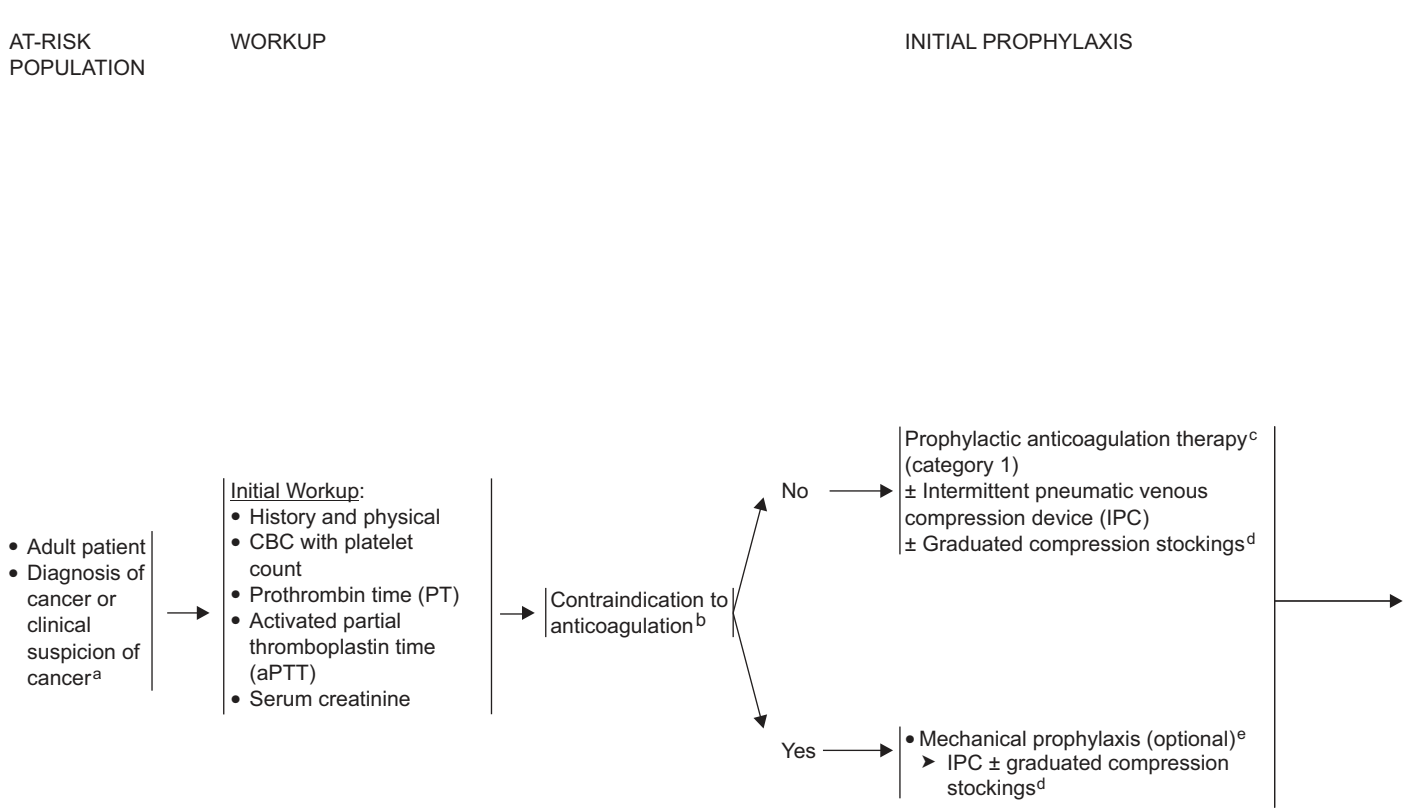
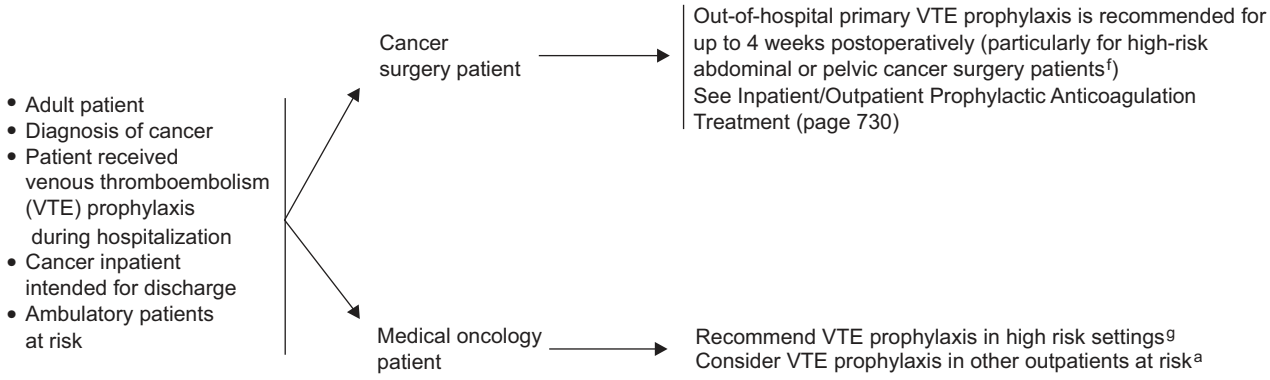
INPATIENT VENOUS THROMBOEMBOLISM PROPHYLAXIS



[a] See VTE Risk Factors in Cancer Patients (page 729).
[b] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (page 730).
[c] Pharmacologic intervention. See Inpatient/Outpatient Prophylactic Anticoagulation Treatment (page 730).
[d] Patient should be appropriately measured for stockings and monitored for adverse effects, especially in immobilized patients with peripheral neuropathy. Dennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet 2009;373:1958-1965.
[e] Most data come from surgical patients; this is an extrapolation to the medical population.

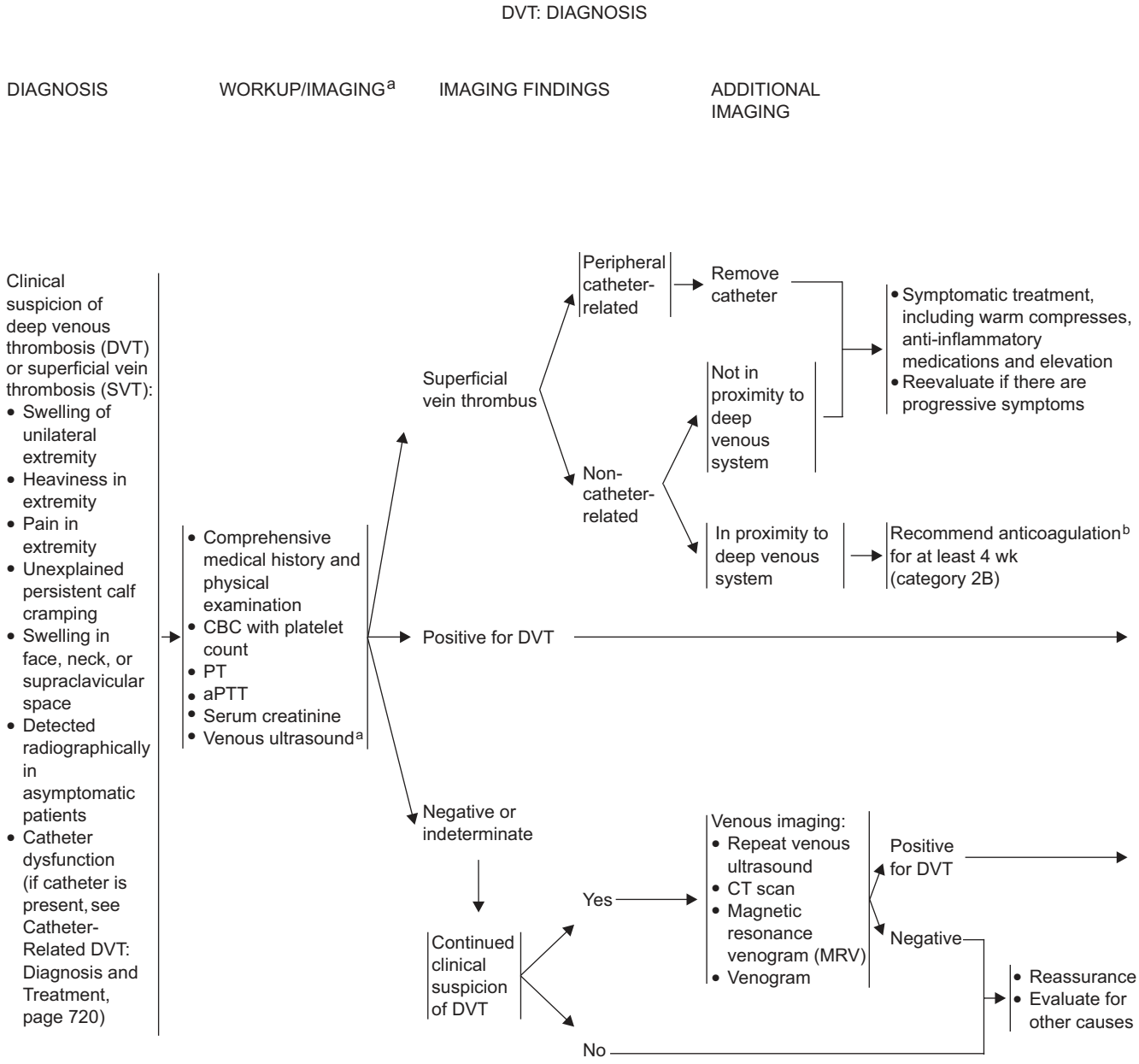
VTE PROPHYLAXIS FOLLOWING DISCHARGE AND
FOR AMBULATORY CANCER PATIENTS AT RISK

AT-RISK POPULATION



[a] See VTE Risk Factors in Cancer Patients (page 729).
[f] High-risk abdominal/pelvic cancer surgery patients include those undergoing surgery for gastrointestinal malignancies, with a previous history of VTE, under anesthesia time of > 2 hours, on bed rest for > 4 days, with advanced-stage disease, or > 60 years.
[g] For high-risk patients receiving highly thrombotic antiangiogenic therapy (i.e., multiple myeloma patients receiving thalidomide/lenalidomide in combination with high-dose dexamethasone [≥ 480 mg/mo] or doxorubicin or multiagent chemotherapy) or for myeloma patients with 2 or more individual or myeloma risk factors (see VTE Risk Factors in Cancer Patients, page 729), recommended prophylaxis is LMWH (e.g., enoxaparin, 40 mg subcutaneous every 24 h) or warfarin (adjusted to INR 2-3). For low-risk myeloma patients with one or no individual or myeloma risk factors, aspirin, 81-325 mg daily, may be used. Aspirin should not be used in nonmyeloma patients for VTE prevention.

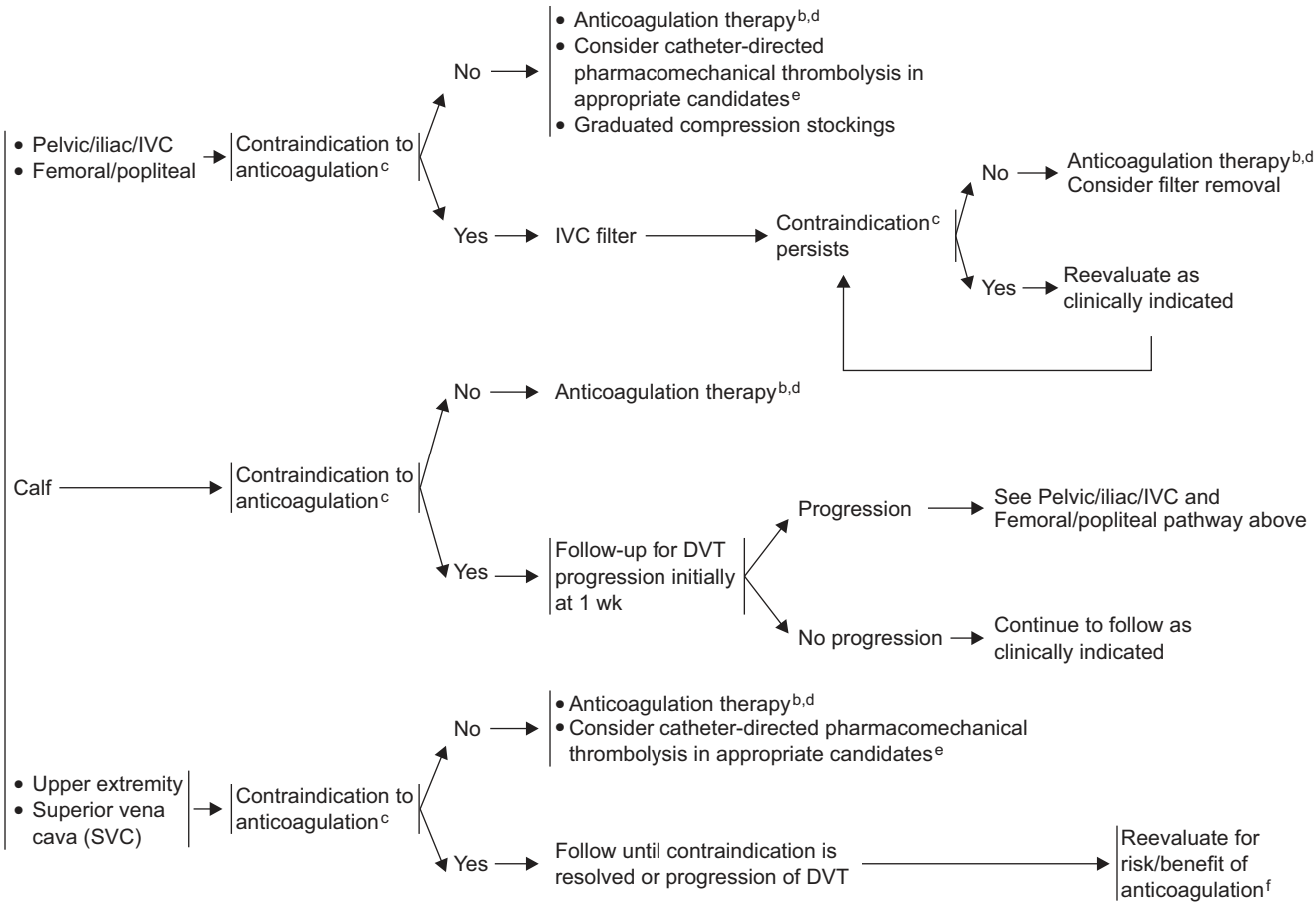
DVT: DIAGNOSIS



[a] Imaging recommendations reflect initial diagnostic workup of an individual not previously diagnosed with DVT.
[b] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (page 731).

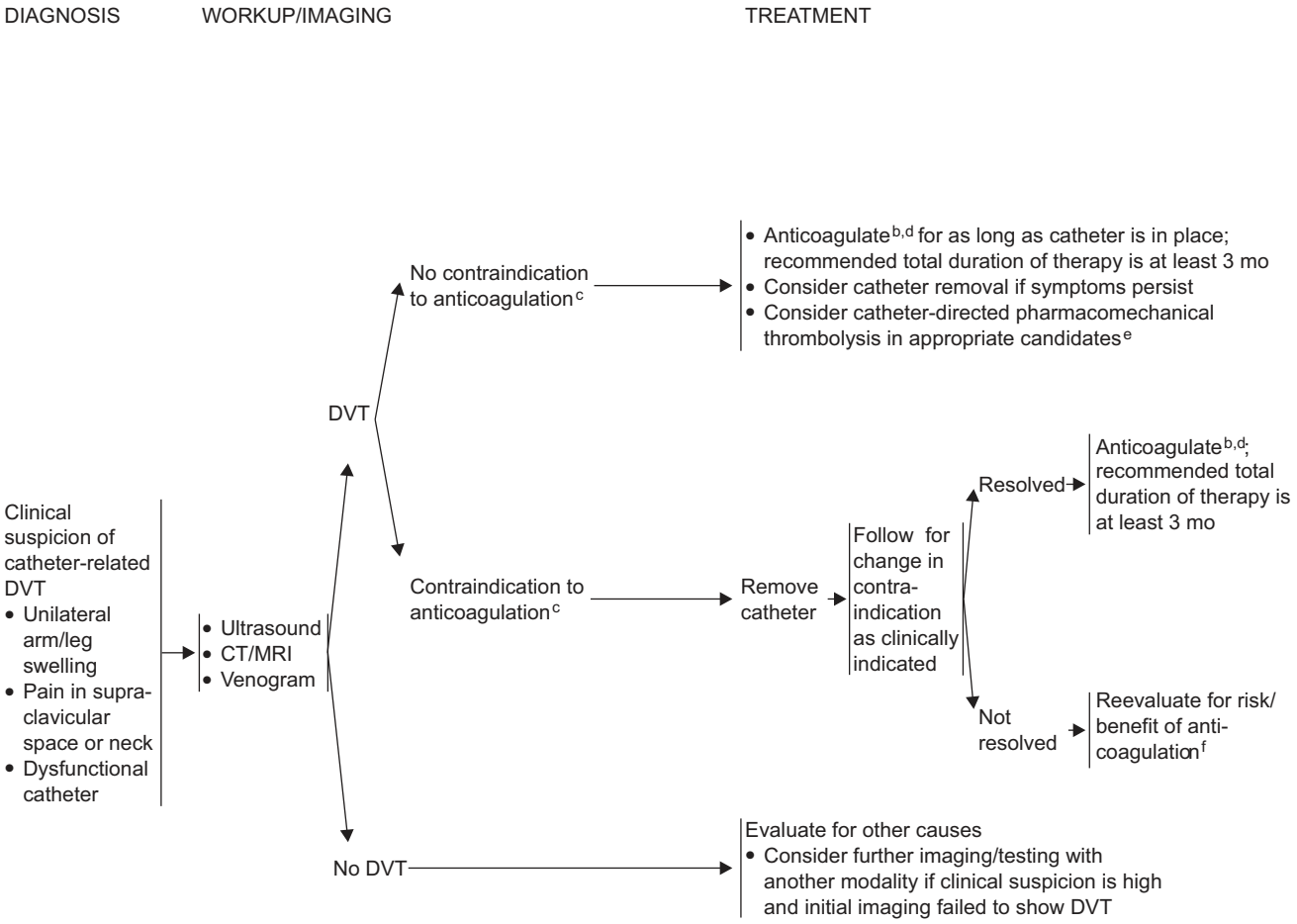
DVT: TREATMENT

DVT LOCATION



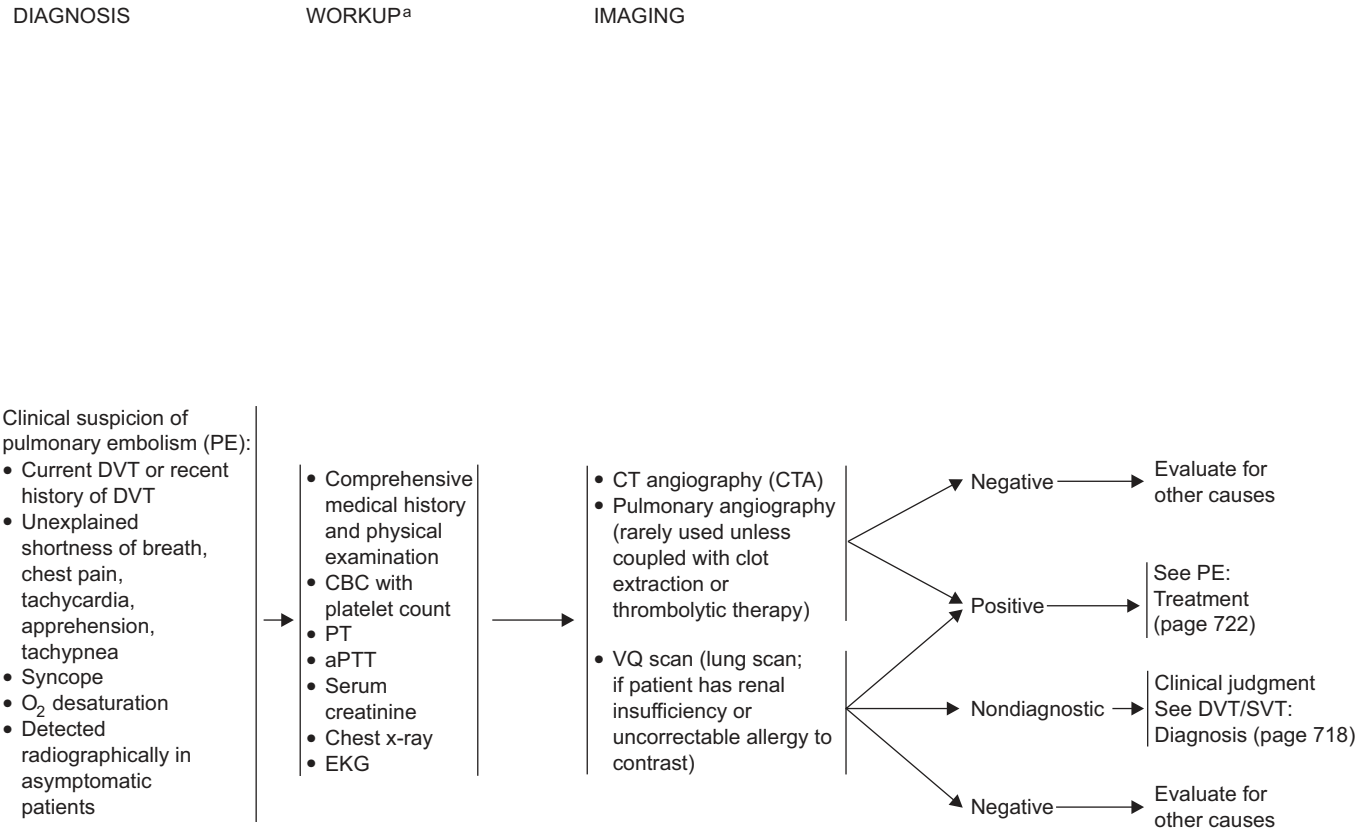
[b] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (page 731).
[c] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (page 730).
[d] See Therapeutic Anticoagulation Failure (page 736), if extension of VTE or new VTE while on recommended anticoagulation therapy
[e] Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues. (Vedantham S, Thorpe PE, Cardella JF, et al. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. J Vasc Interv Radiol 2009;20[7 Suppl]:S227–239.)
[f] See Elements for Consideration in Decision Not To Treat (page 735).

CATHETER-RELATED DVT: DIAGNOSIS AND TREATMENT



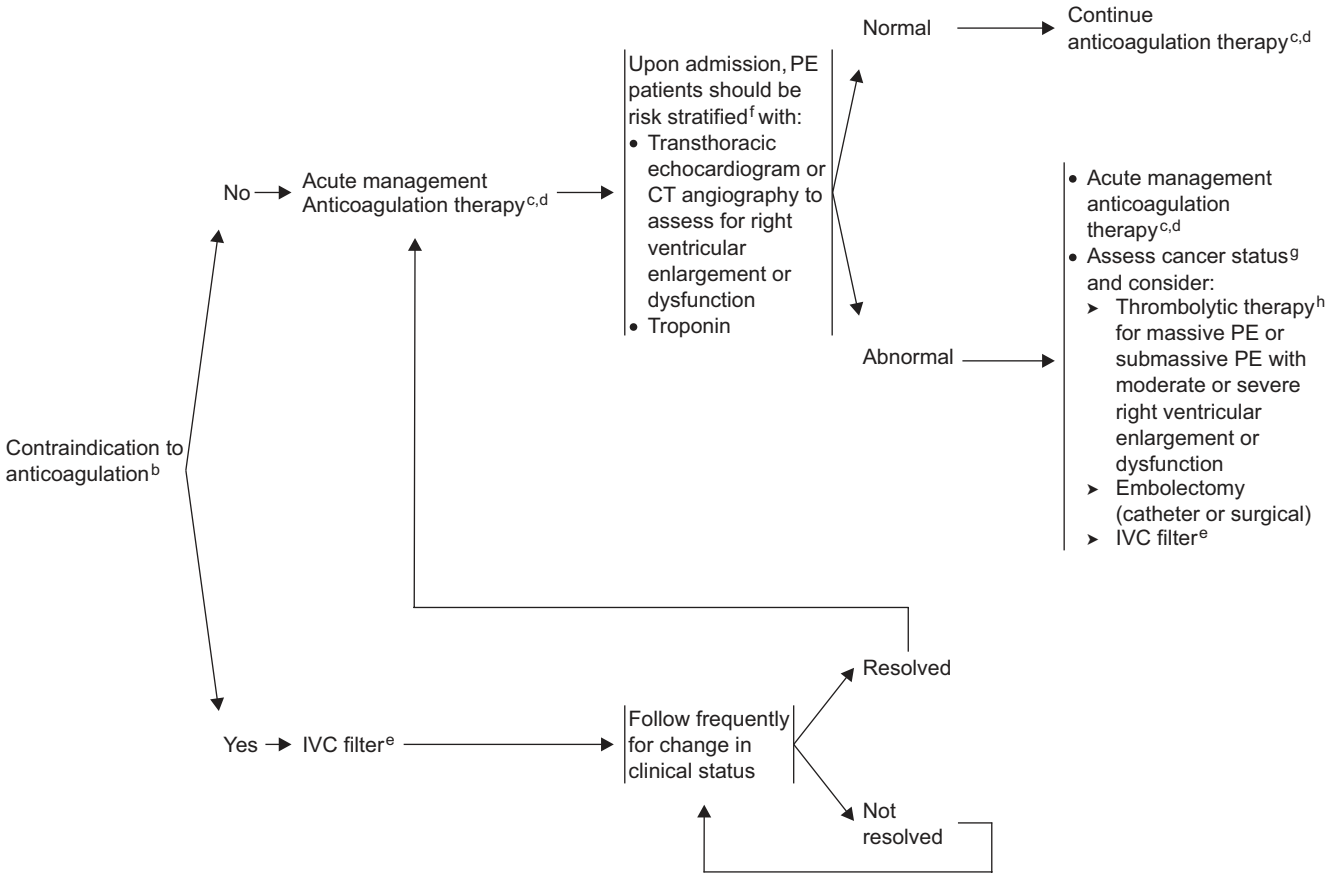
[b] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (page 731).
[c] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (page 730).
[d] See Therapeutic Anticoagulation Failure (page 736), if extension of VTE or new VTE while on recommended anticoagulation therapy
[e] Choice of regimen should be made based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues.
[f] See Elements for Consideration in Decision Not To Treat (page 735).

PE: DIAGNOSIS



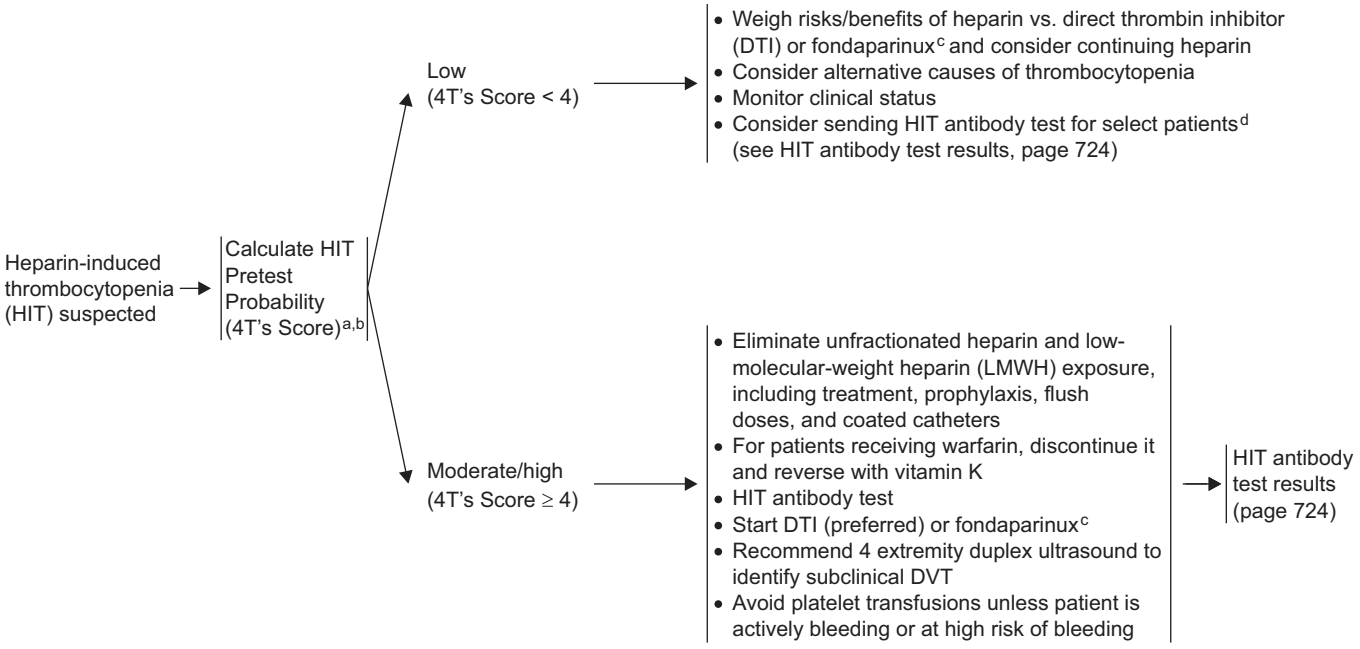
[a]D-dimer has limited efficacy in cancer patients.

PE: TREATMENT



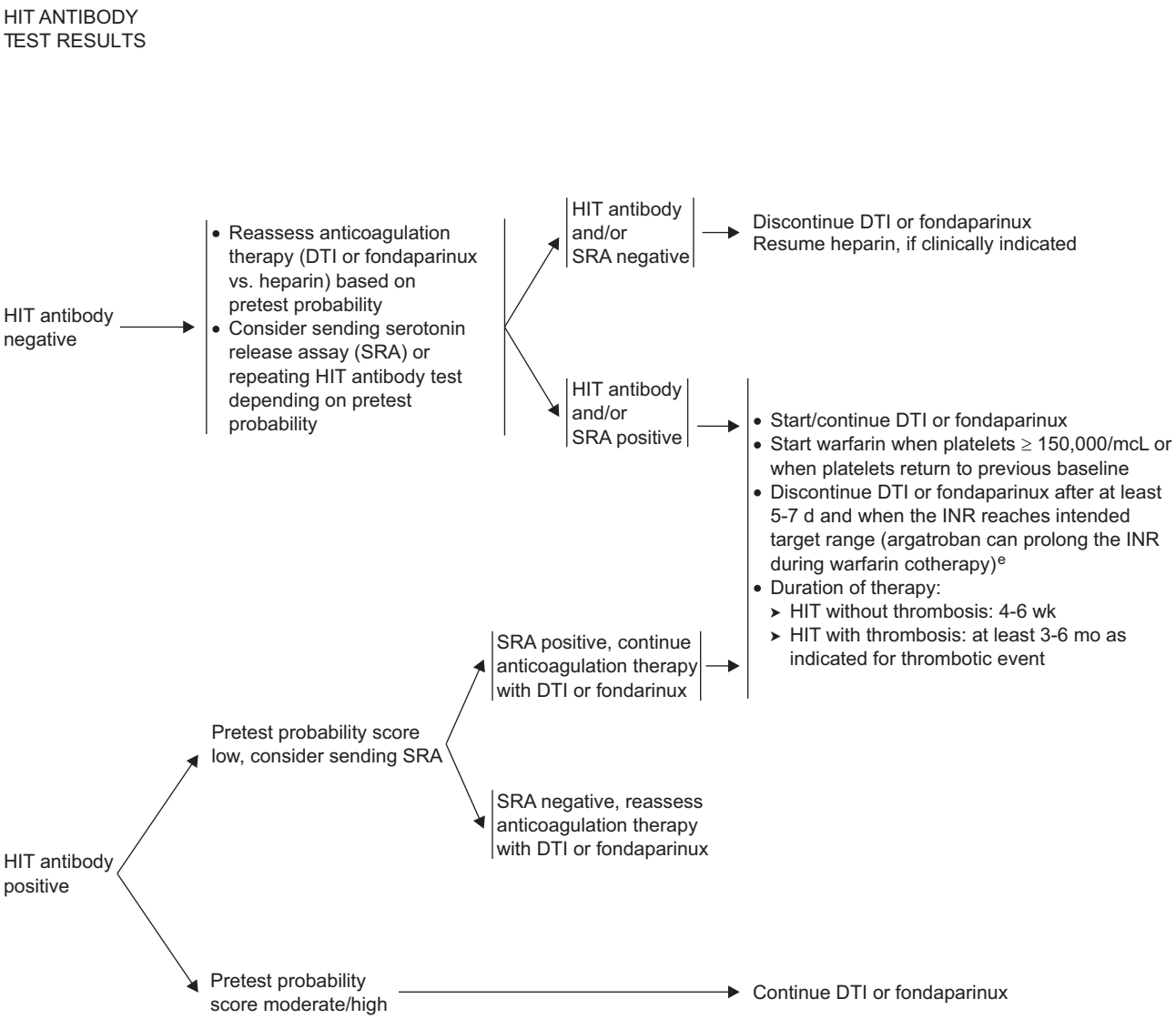
[b] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (page 730).
[c] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (page 731).
[d] See Therapeutic Anticoagulation Failure (page 736), if extension of VTE or new VTE while on recommended anticoagulation therapy
[e] See Clinical Scenarios Warranting Consideration of Filter Placement (page 735).
[f] The Pulmonary Embolism Severity Index (PESI) clinical prediction rule can also be considered, but should not be substituted for the risk stratification procedures indicated above. (Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Scale. Throm Haemost 2008;100:943-948.)
[g] See Elements for Consideration in Decision Not to Treat (page 735).
[h] Alteplase (t-PA), 100 mg IV over 2 h, is the recommended thrombolytic regimen for PE in patients judged to be appropriate candidates for thrombolysis.

DIAGNOSIS AND TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA



[a] See HIT Pretest Probability Score Assessment (page 725).
[b] The 4T's Score has not been validated in cancer patients, so it may have less efficacy, particularly in patients undergoing chemotherapy.
[c] See Therapeutic Options for Heparin-Induced Thrombocytopenia, page 726.
[d] A "Low" pretest probability score combined with a negative antibody test is useful in ruling out a diagnosis of HIT. A positive test increases the suspicion for HIT. Sending for the HIT antibody test should be individualized and based on clinical judgment.

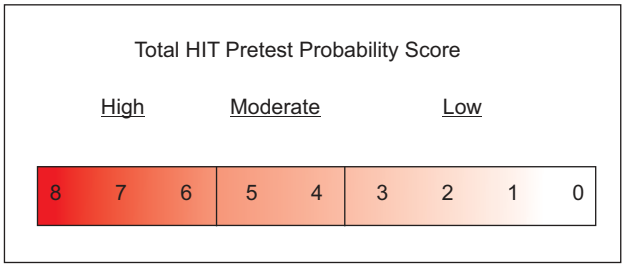
DIAGNOSIS AND TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA (cont.)



[e] See Therapeutic Options for Hepatitis-Induced Thrombocytopenia; section on "warfarin" (page 726).

HIT PRETEST PROBABILITY SCORE ASSESSMENT[1]

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



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

THERAPEUTIC OPTIONS FOR HEPARIN-INDUCED THROMBOCYTOPENIA

Direct Thrombin Inhibitors: Preferred[1]

- Argatroban (half-life 45 minutes - normal liver function) (aPTT ratio 1.5-3)
  - Normal liver function (non-ICU patient): 1 mcg/kg/min adjusted to aPTT ratio (first check in 4 hours)
  - Abnormal liver function (total bilirubin,1.8-3.6 mg/dL; AST/ALT, 150-600 IU/L) or ICU, heart, or multiorgan failure patient: 0.25-0.5 mcg/kg/min
  - Severe liver dysfunction (total bilirubin > 3.6 mg/dL or AST/ALT > 600 IU/L): use lepirudin, bivalirudin, or fondaparinux

- Lepirudin (half-life 80 minutes - normal renal function) (aPTT ratio 1.5-2)[2]
  - Normal renal function (estimated C_{Cr} ≥ 60 mL/min): 0.08 mg/kg/h adjusted to aPTT (first check in 6 hours) (consider 0.2 mg/kg bolus if life or limb-threatening thrombosis)
  - Abnormal renal function
    - Estimated C_{Cr} 30-60 mL/min: 0.04 mg/kg/h
    - Estimated C_{Cr} < 30 mL/min: use argatroban

- Bivalirudin (half-life 25 minutes-normal renal function) (aPTT ratio 1.5-2.5)[2]
  - Consider strongly for patients with combined hepatic and renal dysfunction
  - Dosing: estimated C_{Cr} > 60 mL/min): 0.15 mg/kg/h – adjust to aPTT (first check in 2 hours)
    - Estimated C_{Cr} 45-60 mL/min: 0.1 mg/kg/h
    - Estimated C_{Cr} 31-44 mL/min: 0.075 mg/kg/h
    - Estimated C_{Cr} < 30 mL/min (no renal replacement therapy): 0.05 mg/kg/h
    - Renal replacement therapy or combined hepatic/renal failure: consider argatroban for isolated renal failure or use 0.03 mg/kg/h

Indirect Factor Xa Inhibitor[3] (category 2B)

- Fondaparinux (half-life 17-21 hours - normal renal function)
  - For patients with C_{Cr} < 50 mL/min (clearance 40% lower): consider alternative agent
  - For patients with C_{Cr} < 30 mL/min: avoid
  - Dose
    - 5 mg subcutaneous daily (body weight < 50 kg)
    - 7.5 mg subcutaneous daily (body weight 50-100 kg)
    - 10 mg subcutaneous daily (body weight > 100 kg)

Warfarin

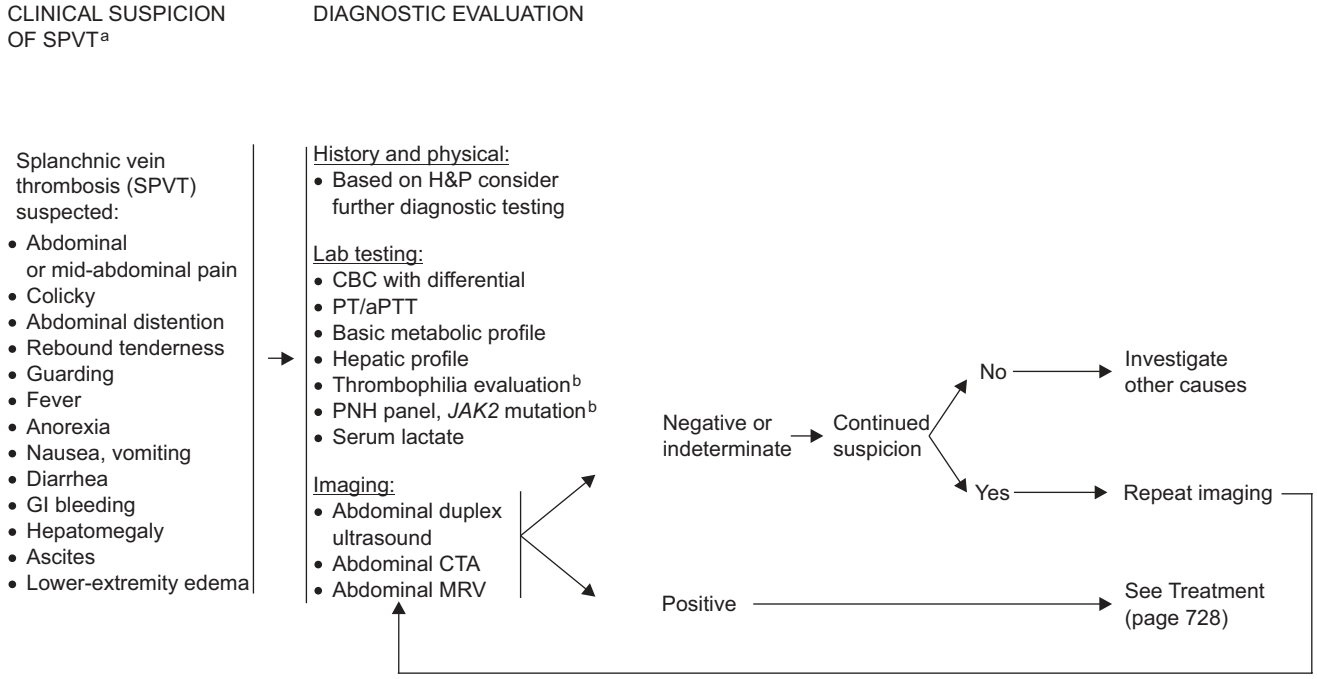
- Initiate once platelets ≥ 150,000/mcL or return to baseline
- Initial dose 5 mg (consider lower dose for patients: age > 75 years, CYP2C9 inhibitors, poor oral intake, liver disease)
- DTI/fondaparinux-warfarin overlap should be at least 5 days: continue warfarin until INR ≥ 2 for 24 hours
- Argatroban can increase the INR substantially during warfarin cotherapy therefore a higher target INR (~ 4.0) should be achieved before argatroban is discontinued. Bivalirudin and lepirudin, to a lesser extent, slightly prolong the INR during cotherapy
- INR and aPTT should be repeated within 3-6 hours after argatroban has been discontinued
- Alternatively, chromogenic factor X activity, which is not affected by DTIs, can be used to monitor warfarin during cotherapy
- Treat for at least 1 mo (no thrombosis) or at least 3-6 mo as dictated by thrombotic event

Platelet Transfusions

- Generally not necessary unless active bleeding or invasive procedure necessary and platelet count < 50,000/mcL

[1] A direct thrombin inhibitor is preferred over fondaparinux for the immediate treatment of patients with acute HIT with thrombosis.
[2] Patients reexposed to lepirudin within the past 3 mo may be susceptible to anaphylaxis. Anaphylaxis has also occurred with bivalirudin.
[3] Used as a second-line agent. Fondaparinux has been rarely associated with HIT.

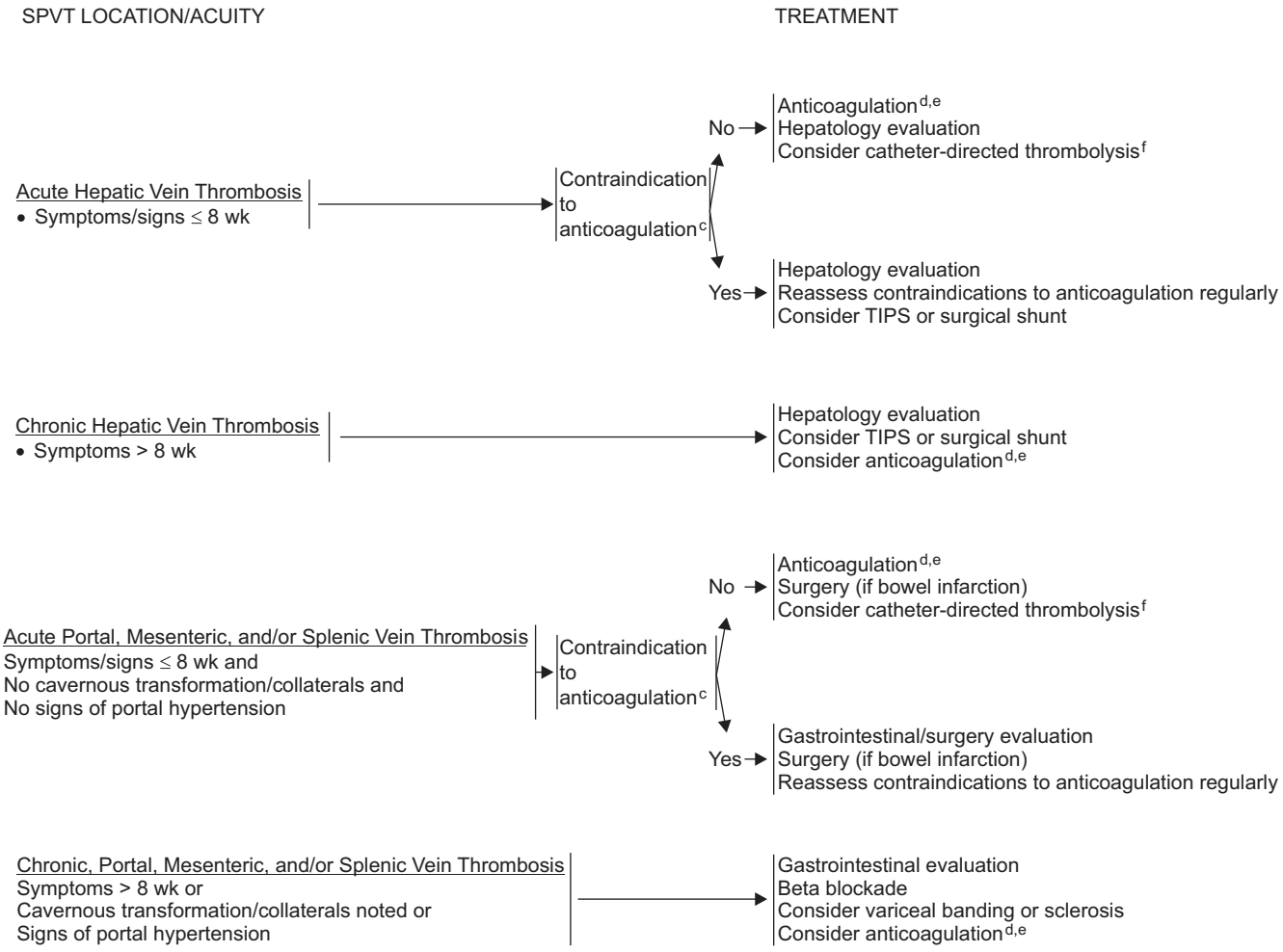
SPVT: DIAGNOSIS



[a] Risk Factors relevant to cancer population for SPVT:
- Recent abdominal surgery (e.g., splenectomy)
- Cancer
- Abdominal mass
- Pancreatitis
- Cirrhosis
- Thrombophilia
- Exogenous estrogens
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Myeloproliferative disorder (polycythemia vera, essential thrombocytosis)

[b] Consider performing thrombophila evaluation, PNH panel, and *JAK2* mutation testing if SPVT is diagnosed on imaging.

SPVT: TREATMENT



[c] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (page 730).
[d] Weigh risks/benefits of anticoagulation, particularly for chronic thromboses. Duration of anticoagulation at least 6 mo for triggered events (e.g., postsurgical); indefinite if active cancer, thrombophilic state, or idiopathic thrombosis.
[e] See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (page 731).
[f] Decision to offer thrombolysis should be based on local availability/expertise, location of thrombus, and risk of bleeding. Regimen should be selected based on institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues.

VTE RISK FACTORS IN CANCER PATIENTS

General Patient Risk Factors

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

High-Risk Outpatients on Chemotherapy, Based on Combinations of the Following Risk Factors[1,2]

- Active cancers associated with high incidence of VTE: stomach, pancreas, lung, lymphoma, gynecologic, bladder, and testicular
- Prechemotherapy platelet count > 300,000/mcL
- Prechemotherapy WBC > 11,000/mcL
- Hemoglobin < 10 g/dL
- Use of erythropoietic stimulating agents
- Body mass index ≥ 35 kg/m^2
- Prior VTE

Treatment-Related Risk Factors

- Major surgery
- Central venous catheter/IV catheter
- Chemotherapy, especially use of:
  - Bevacizumab
  - Thalidomide/lenalidomide plus high-dose dexamethasone
- Exogenous estrogen compounds
  - Hormone replacement
  - Contraceptives
  - Tamoxifen/raloxifene
  - Diethylstilbestrol

Modifiable Risk Factors

- Smoking, tobacco
- Obesity
- Activity level/exercise

Multiple Myeloma Risk Factors[3]

- M spike > 1.6 g/dL
- Progressive disease
- Hyperviscosity

[1] Additional prospective randomized data are required to assess the benefit and safety of routine VTE prophylaxis in a cancer outpatient population with a favorable risk/benefit ratio. Listed risk factors are limited to cancer populations included in recent prospective, observational studies of solid tumor or lymphoma outpatients undergoing chemotherapy (Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-4907).

[2] Mandalà M, Prins M, Labianca C, et al. Acquired and inherited risk factors for developing venous thromboembolism in cancer patients receiving adjuvant chemotherapy: a prospective trial. Ann Oncol 2010;21:871-876.

[3] Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-423.

CONTRAINDICATIONS TO PROPHYLACTIC OR THERAPEUTIC ANTICOAGULATION TREATMENT

- Recent central nervous system 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 (e.g., factor VIII deficiency, severe liver disease)
  - Elevated PT or aPTT (excluding lupus inhibitors)
- Spinal anesthesia/lumbar puncture
- High risk for falls (head trauma)

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

- LMWH[4] (category 1 for inpatient):
  - Dalteparin, 5000 units subcutaneous daily
  - Enoxaparin, 40 mg subcutaneous daily
  - Tinzaparin,[5] 4500 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: 5000 units subcutaneous 3 times daily (category 1 for inpatient)
- Aspirin, 81-325 mg/d (for low-risk multiple myeloma outpatients only)[7]
- Warfarin (adjusted to INR 2-3)[8]

For Diagnosis and Treatment of Heparin-Induced Thrombocytopenia, see page 723

[1] Agent selection based on:
- Renal failure (C_{cr} < 30 mL/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.

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

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

[5] Tinzaparin should be avoided in patients > 70 y with renal insufficiency. Refer to the FDA Web site for additional information (http://www.fda.gov/medwatch/safety/2008/safety08.htm#Innohep).

[6] Fondaparinux is contraindicated in patients with C_{cr} < 30 mL/min. It should be used with caution in patients with moderate renal insufficiency (C_{cr} 30-50 mL/min), weight < 50 kg, or age > 75 y.

[7] Use only for lower-risk multiple myeloma outpatients with one or no individual or myeloma risk factors (see VTE Risk Factors in Cancer Patients, page 729).

[8] Warfarin (INR 2-3) or LMWH (e.g., enoxaparin, 40 mg subcutaneous every 24 hours) are prophylaxis options for select high-risk myeloma outpatients receiving highly thrombotic antiangiogenic therapy (i.e., multiple myeloma patients receiving thalidomide/lenalidomide in combination with high-dose dexamethasone [≥ 480 mg/mo] or doxorubicin or multiagent chemotherapy) or for myeloma patients with ≥ 2 individual or myeloma risk factors (see VTE Risk Factors in Cancer Patients, page 729).

Venous Thromboembolic Disease Version 2:2011

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

Acute Management (at Diagnosis or During Diagnostic Evaluation)

- LMWH[4]
  - Dalteparin (200 units/kg subcutaneous daily)[5]
  - Enoxaparin (1 mg/kg subcutaneous every 12 hours)
  - Tinzaparin[6] (175 units/kg subcutaneous daily)
- Fondaparinux[7] (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/h, target aPTT of 2-2.5 x control or per hospital SOP)

Chronic Management:[1]

- LMWH[4] (category 1) is preferred for the first 6 mo as monotherapy without warfarin in patients with proximal DVT or PE and prevention of recurrent VTE in patients with advanced or metastatic cancer
- Warfarin (2.5-5 mg every day initially, subsequent dosing based on INR value; target INR 2-3)
  - If warfarin is selected for chronic anticoagulation, initiate warfarin concurrently with the parenteral agent used for acute therapy and continue both therapies for at least 5 days and until the INR $\geq$ 2 for 24 hours.
  - During the transition to warfarin monotherapy, the INR should be measured at least twice weekly. Once the patient is on warfarin alone, the INR should be measured initially at least once weekly. Once the patient is on a stable dose of warfarin with an INR between 2 and 3, INR testing can be gradually decreased to a frequency no less than once monthly.

Duration of Anticoagulation as Recommended by Guideline:

- 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; recommended total duration of therapy is at least 3 mo

For Diagnosis and Treatment of Heparin-Induced Thrombocytopenia, see page 723
For Reversal of Anticoagulation, see pages 732-734

[1] Agent selection based on: renal failure (C_{cr} < 30 mL/min), inpatient/outpatient, FDA approval, cost, ease of administration, monitoring, and 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. Kearon C, Kahn SR, Agnelli G, 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.

[3] After initiation of heparin: hemoglobin, hematocrit, and platelet count every 2-3 days for the first 14 days and every 2 wk thereafter or as clinically indicated.

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

[5] For chronic treatment, dalteparin, 150 units/kg/d, after 30 days. Although each of the LMWHs have been studied in randomized controlled trials in cancer patients, the efficacy of dalteparin in this population is supported by the highest quality evidence and it is the only LMWH approved by the FDA for this indication. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-153.

[6] Tinzaparin should be avoided in patients > 70 y with renal insufficiency Refer to the FDA Web site for additional information (http://www.fda.gov/medwatch/safety/2008/safety08.htm#Innohep).

[7] Fondaparinux is contraindicated in patients with C_{cr} < 30 mL/min. It should be used with caution in patients with moderate renal insufficiency (C_{cr} 30-50 mL/min), weight < 50 kg, or age > 75 y.

REVERSAL OF ANTICOAGULATION

In the event of bleeding or the need for urgent/emergent invasive procedures, anticoagulant effect must be reversed promptly. The reversal guidelines for different anticoagulants are displayed in the table below:

Anticoagulant	Reversal	Precautions/Additional Considerations
Unfractionated heparin (half-life 1 hour)	• Protamine, 1 mg per 100 units of heparin (taking into account UFH ~1-hour half-life) by slow IV infusion (no faster than 5 mg/min) • Follow aPTT closely • Maximum dose: 50 mg (example: patient bleeds immediately after 5000 unit bolus is given 50 mg of protamine. Patient on 1250 units per hour bleeds and is given 24 mg of protamine to reverse the heparin remaining from the last 4 hours of the infusion)	• Protamine can cause anaphylaxis if administered too rapidly • Patients with fish allergies, previous exposure to protamine (e.g., NPH insulin), or vasectomized or infertile men are at increased risk • Excessive protamine (protamine: heparin ratios > 1.3:1) are associated with platelet dysfunction and decreased thrombin activity, resulting in bleeding • Protamine will reverse no more than 60% of the activity of LMWH, regardless of dose
LMWH (half-life 3-7 hours)	• Protamine, 1 mg/mg of enoxaparin or 1 mg per 100 units of dalteparin or tinzaparin within 8 hours of dose • Protamine, 0.5 mg/mg of enoxaparin or 0.5 mg per 100 units of dalteparin or tinzaparin if dose administered > 8 hours prior • If > 12 hours since dose, consider clinical scenario (e.g., LMWH dose, renal function, bleeding severity) in deciding whether protamine is indicated • Administer protamine by slow IV infusion (no faster than 5 mg/min) • Maximum dose: 50 mg	

Cont. on facing page

The Reversal of Anticoagulation tables comprise data from the following references:
- Crowther MA, Warkentin TE. Bleeding risk and management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood 2008;111:4871-4879.
- Ansell J, Hirsh J, Hylek E, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133(6 Suppl):160S-198S.
- Schulman S, Bjisterveld NR. Anticoagulants and their reversal. Transfus Med Rev 2007;21:37-48.
- Holland L, Warkentin TE, Rafaai M, et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. Transfusion 2009;49:1171-1177.
- Koster A, Buz S, Krabatsch T, et al. Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary artery bypass grafting: assessment of different filtration strategies. J Card Surg 2008;23:655-658.

REVERSAL OF ANTICOAGULATION (cont.)

Anticoagulant	Reversal	Precautions/Additional Considerations
Warfarin (Effective half-life 20-60 hours) • INR < 5, no bleeding	• Hold warfarin dose	
• INR 5-9, no bleeding	• Hold warfarin dose • Consider small dose of oral vitamin K_1 (phytonadione), 1-2.5 mg, in patients at high-risk of bleeding • Follow INR closely	Vitamin K_1 (phytonadione) should not be given subcutaneously because its absorption is erratic and delayed compared to oral or IV vitamin K_1
• INR > 9, no bleeding	• Hold warfarin dose Consider small dose of oral vitamin K_1 (phytonadione), 2.5 mg, especially in patients at high-risk of bleeding • Follow INR closely	
• Serious bleeding at any INR • Life-threatening bleeding	• Hold warfarin dose • Administer vitamin K_1 (phytonadione), 10 mg IV, over 60 minutes • Administer 3-factor prothrombin complex concentrate (PCC), 25-50 units/kg, + fresh frozen plasma (FFP), 2-3 units or FFP, 15 mL/kg (if no PCC available) or rhFVIIa, 10-90 mcg/kg IV • Monitor INR closely and repeat PCC or FFP if necessary	• Administer IV vitamin K_1 (phytonadione) slowly (< 1 mg/min). Rapid administration of IV vitamin K_1 associated with a higher risk of anaphylaxis (risk ~1 in 3000 doses) • Monitor vital signs closely • PCC and rhFVIIa have been associated with thromboembolic events

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The Reversal of Anticoagulation tables comprise data from the following references:
- Crowther MA, Warkentin TE. Bleeding risk and management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood 2008;111:4871-4879.
- Ansell J, Hirsh J, Hylek E, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133(6 Suppl):160S-198S.
- Schulman S, Bjisterveld NR. Anticoagulants and their reversal. Transfus Med Rev 2007;21:37-48.
- Holland L, Warkentin TE, Refaai M, et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. Transfusion 2009;49:1171-1177.
- Koster A, Buz S, Krabatsch T, et al. Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary artery bypass grafting: assessment of different filtration strategies. J Card Surg 2008;23:655-658.

REVERSAL OF ANTICOAGULATION (cont.)

Anticoagulant	Reversal	Precautions/Additional Considerations
Fondaparinux (half-life 17-21 hours)	rhFVIIa, 90 mcg/kg IV, intended for reversal of therapeutic doses of fondaparinux	rhFVIIa has been associated with thromboembolic events
Direct thrombin inhibitors* • Bivalirudin (half-life 25 min - normal renal function)	No specific antidote exists. Beneficial effects have been ascribed to the following: 1. rhFVIIa, 90 mcg/kg IV 2. Hemodiafiltration with polysulfone membranes is more effective than hemofiltration 3. DDAVP, 0.3 mcg/kg IV 4. Cryoprecipitate, 10 units IV 5. FFP, 15 mL/kg 6. Antifibrinolytics (aminocaproic acid, 0.1 g/kg IV followed by 1 g/h, or tranexamic acid, 10 mg/kg IV every 6 hours)	• Limited data exist to support all reversal strategies for bivalirudin • Repeated doses (> 3 or 4 doses) of DDAVP associated with tachyphylaxis and hyponatremia
• Lepirudin normal renal (half-life 80 min - function)	No specific antidote exists. Beneficial effects have been ascribed to the following: 1. rhFVIIa, 90 mcg/kg IV 2. Hemofiltration using polysulfone membranes 3. DDAVP, 0.3 mcg/kg IV 4. Cryoprecipitate, 10 units IV 5. FFP, 15 mL/kg 6. Antifibrinolytics (aminocaproic acid, 0.1 g/kg IV followed by 1 g/h, or tranexamic acid, 10 mg/kg IV every 6 hours)	• Limited data exist to support all reversal strategies for lepirudin • Repeated doses (> 3 or 4 doses) of DDAVP associated with tachyphylaxis and hyponatremia
• Argatroban (half-life 45 min - normal hepatic function)	No specific antidote exists. Beneficial effects have been ascribed to the following: 1. rhFVIIa, 90 mcg/kg IV 2. DDAVP, 0.3 mcg/kg IV 3. Cryoprecipitate, 10 units IV 4. FFP, 15 mL/kg 5. Antifibrinolytics (aminocaproic acid, 0.1 g/kg IV followed by 1 g/h, or tranexamic acid, 10 mg/kg IV every 6 hours	• Limited data exist to support all reversal strategies for argatroban • Repeated doses (> 3 or 4 doses) of DDAVP associated with tachyphylaxis and hyponatremia

*Limited information is available on the clinical efficacy of all these proposed reversal strategies. For life-threatening bleeding, the NCCN panel currently favors use of rhFVIIa as the first-line agent. Hemofiltration or hemodiafiltration can accelerate the clearance of lepirudin and bivalirudin.

The Reversal of Anticoagulation tables comprise data from the following references:
- Crowther MA, Warkentin TE. Bleeding risk and management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood 2008;111:4871-4879.
- Ansell J, Hirsh J, Hylek E, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133(6 Suppl):160S-198S.
- Schulman S, Bjisterveld NR. Anticoagulants and their reversal. Transfus Med Rev 2007;21:37-48.
- Holland L, Warkentin TE, Refaai M, et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. Transfusion 2009;49:1171-1177.
- Koster A, Buz S, Krabatsch T, et al. Effect of modified ultrafiltration on bivalirudin elimination and postoperative blood loss after on-pump coronary artery bypass grafting: assessment of different filtration strategies. J Card Surg 2008;23:655-658.

ELEMENTS FOR CONSIDERATION IN DECISION NOT TO TREAT

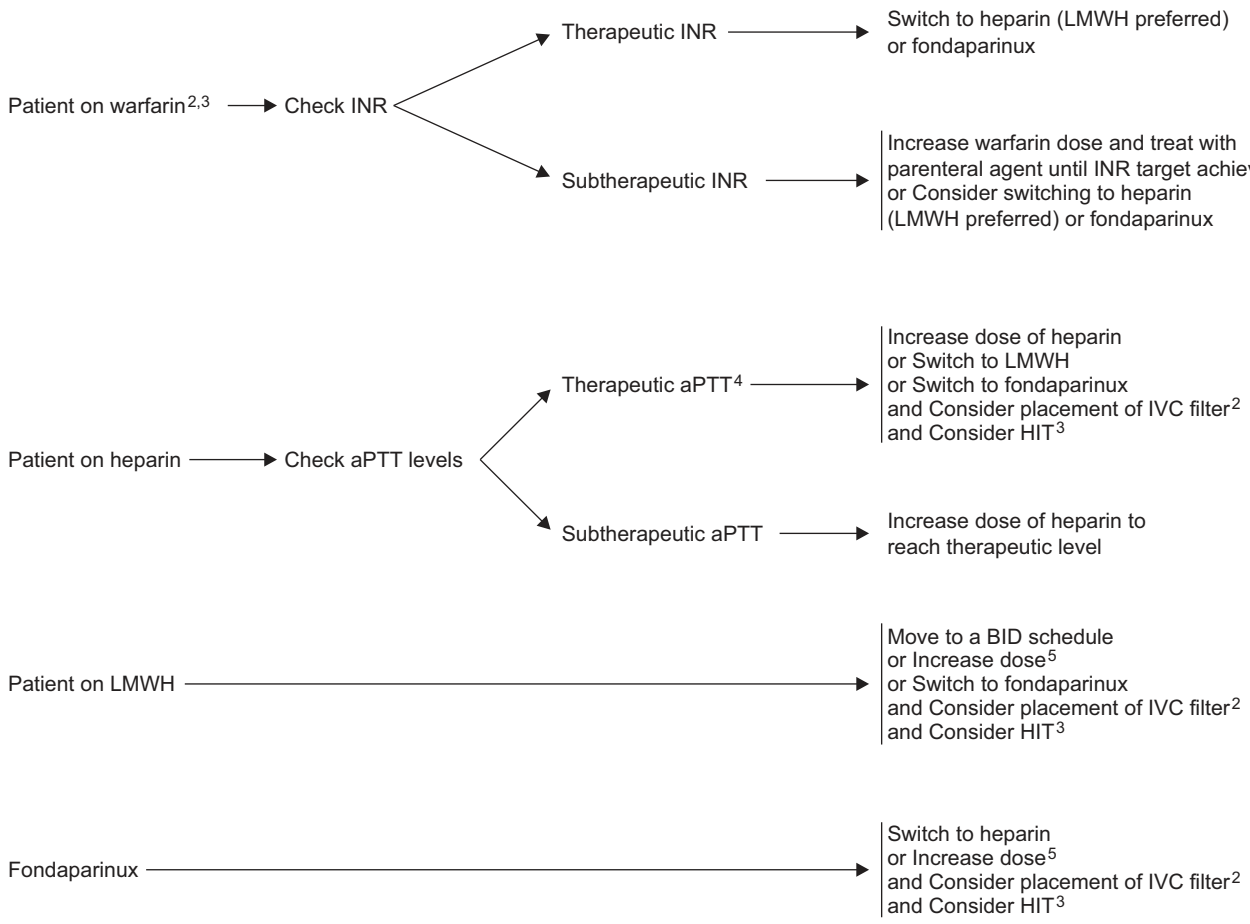
- Patient refusal
- No therapeutic advantage
  - Limited survival
  - High risk
  - No planned oncologic intervention
- No palliative benefit (e.g., alleviate dyspnea, prevent leg swelling)
- Unreasonable burden of anticoagulation treatment
  - Painful injections
  - Frequent monitoring with phlebotomy

CLINICAL SCENARIOS WARRANTING CONSIDERATION OF FILTER PLACEMENT

- Contraindication to anticoagulation[1]
- Failure of anticoagulation[2]
- Patient noncompliance 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 (page 730).
[2] See Therapeutic Anticoagulation Failure (page 736).

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 (page 731).
[2] If failure of anticoagulation involves a PE or central DVT progression, placement of a filter is recommended to prevent fatal PE, and consider thrombolysis should be considered for high-risk patients (for submassive or massive PE or massive DVT that is life- or limb-threatening).
[3] Evaluate for HIT (page 723). If clinical suspicion of HIT is high, see page 723.
[4] Therapeutic aPTT range based on hospital SOP range or 2.0-2.5 x control, if local ranges are unavailable.
[5] Although data are limited, doses are generally increased by 25%.

Text continued from p. 715

The occurrence of VTE has been reported to increase the likelihood of death in cancer patients by 2- to 6-fold.[9–13] For example, patients with gynecologic cancer and PE were found to have a 6-fold increased risk of death at 2 years compared with similar patients without PE.[12] Furthermore, VTE has been reported to be the most common cause of death at 30-day follow-up among cancer patients undergoing surgery.[14]

The critical need for the development of clinical practice guidelines focusing specifically on VTE in patients with cancer is further underscored by the results of practice surveys of VTE prophylaxis. The Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey noted that only 50% of surgical oncologists and 5% of medical oncologists routinely used VTE prophylaxis in their patients.[15] Similar results were documented in the multinational IMPROVE and ENDORSE registries of hospitalized medically ill patients, in which only 45% of patients with cancer received any form of VTE prophylaxis.[16,17] 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 occur in nonsurgical patients.[18]

To address the important problem of VTE in cancer patients, the NCCN initially convened a panel of experts in 2005 and then annually thereafter. The interdisciplinary NCCN Venous Thromboembolic Disease Panel includes medical and surgical oncologists, hematologists, cardiologists, internists, interventional radiologists, nurses, and pharmacists. These NCCN Guidelines discuss the diagnosis, prevention, 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 risk factors for VTE are common to patients with cancer,[19,20] and can be grouped into 3 general categories: patient-related factors (both intrinsic and extrinsic), cancer-related factors, and treatment-related factors. Cancer patients probably have risk factors from all 3 categories, and the VTE risk conferred by a single risk factor cannot be evaluated in isolation from the others.

More advanced age, a common characteristic of many cancer patients, was shown to be associated with an increased risk of VTE in some clinical settings,[1,14,21] and obesity was also identified as a risk factor.[21–24] Evidence also shows that prechemotherapy thrombocytosis,[24–26] leukocytosis,[24] and hemoglobin level less than 10 g/dL[24,25] are predictive of VTE in patients undergoing chemotherapy, although the association of anemia with VTE may be complicated by the use of erythropoietic stimulating agents. Acquired risk factors for VTE include a history of VTE and certain hypercoagulable conditions, such as pregnancy. A history of VTE has been identified in several studies as an independent risk factor for developing a subsequent VTE.[14,23,26–29] Moreover, recurrent VTE was found to be more common among patients with cancer; for example, 12-month cumulative incidences of 20.7% and 6.8% of recurrent VTE were reported for patients with and without cancer, respectively, undergoing anticoagulant treatment.[30] Although factor V Leiden and prothrombin mutations were identified in 3.7% and 2.6%, respectively, of patients with breast or colon cancer undergoing adjuvant chemotherapy in a recent prospective observational study, these inherited risk factors were not associated with an increased risk of VTE among cancer patients.[26] Several other patient-related VTE risk factors, although not exclusive to cancer patients, are commonly found in this population. These include hospitalization, other medical comorbidities (e.g., infection), poor performance status, and prolonged immobilization.[3]

Several VTE risk factors are exclusive to cancer patients, including the presence of malignancy, chemotherapy and extrinsic vascular compression due to cancer-associated regional bulky lymphadenopathy. Results from 2 population-based, case-control studies showed that the presence of cancer increased the risk of VTE by 4- and 7-fold.[31,32] An increased risk of VTE in patients with cancer has also been supported by the results of other studies.[27,33] Furthermore, researchers have reported cancer as the cause of approximately 20% of the VTE cases seen in the community,[3] and a recent cancer diagnosis and the occurrence of advanced malignancies and distant metastases also increase VTE risk.[2,23,31,34,35] For example, Blom et al.[31] reported an adjusted odds ratio (OR) of 19.8 for VTE risk in patients with solid tumors with distant metastases compared with those without. In addition, tumor histology has been shown to influence the risk of VTE in patients. Several studies have evaluated the associ-

ation between different types of cancer and the risk of developing a VTE.[1,2,9,31,33,36] For example, pancreatic cancer[1,2,9,33,34,36] and brain tumors[1,2,31,37–39] were associated with a high risk of VTE in several studies. Adenocarcinomas seem to be associated with a higher risk compared with squamous cell cancers.[33] Although differences in study designs make it difficult to compare VTE rates according to specific type of malignancy, other cancers that have been associated with an increased risk of VTE include those of the stomach, kidney, uterus, lung, ovary, bladder, and testis.[1,21,31] In addition, an increased risk of VTE has been observed in certain hematologic malignancies, such as lymphoma, acute leukemia, and multiple myeloma.[1,40,41] Patients with high-grade lymphoma and acute promyelocytic leukemia seem to be at higher risk than those with other forms of lymphoma or leukemia.[40] In a study of patients with high-grade non-Hodgkin's lymphoma, disease-related venous compression was shown to be the most common cause of VTE.[42]

Several factors associated with increased VTE risk in patients with myeloma include the diagnosis of multiple myeloma itself, hyperviscosity, and treatment with thalidomide- or lenalidomide-based combination regimens (combined with high-dose dexamethasone, doxorubicin, or multiagent chemotherapy).[41] Further validation of the influence of these risk factors on VTE rates in patients with myeloma is warranted. In contrast, breast cancer was associated with a relatively low risk for VTE in some studies.[1,10,43] Nevertheless, because of the relatively high prevalence of breast cancer, the occurrence of VTE in patients with breast cancer is not uncommon.[38] Furthermore, the risk of VTE was shown to increase by 6-fold when patients with metastatic breast cancer were compared with those with localized disease.[10]

Treatment-related risk factors include surgery, the presence of a CVAD, and administration of chemotherapy and other systemic treatments. For example, Heit et al.[32] reported nearly 22- and 8-fold increases in risks for the development of VTE in patients hospitalized or confined to a nursing home with and without recent surgery, respectively, compared with noninstitutionalized patients who had not undergone recent surgery.

Several 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, these NCCN Guidelines describe some of the evidence for the association of 3 representative classes of cancer drugs (cytotoxic chemotherapy regimens, hormone therapy with estrogenic compounds, and antiangiogenic agents) with increased VTE risk.

The association of cytotoxic chemotherapy with the development of VTE in cancer patients has been shown in several studies.[24,25,44] For example, in one population-based, case-control study, ORs of 6.5 and 4.1 for development of VTE were determined when cancer patients receiving and not receiving chemotherapy, respectively, were compared with patients without a malignant neoplasm.[32] In another retrospective study, the annual incidence of VTE was 10.9% in patients with colorectal cancer treated with chemotherapeutic regimens.[8] Khorana et al.[24] published a risk assessment model to estimate VTE risk in ambulatory cancer patients undergoing chemotherapy. This risk assessment model was recently validated and extended by Ay et al.,[45] who identified D dimer and P selectin as additional discriminatory risk factors for VTE in ambulatory cancer patients. However, these laboratory tests are not routinely measured in cancer patients, and therefore their inclusion in routine thrombotic risk assessment should be predicated on their validation in future studies. The risk factors identified by Khorana et al.,[24] which formed the basis for the risk assessment models, set the stage for prospective, confirmatory randomized clinical trials evaluating the risks and benefits of risk-targeted VTE prophylaxis in ambulatory cancer patients undergoing chemotherapy.

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.[46–50] Use of estrogenic compounds, such as hormone replacement therapy[51,52] or oral contraceptive agents,[53,54] has also been associated with increased risk of developing VTE. Diethylstilbestrol phosphate in combination with doxorubicin for the treatment of hormone-refractory prostate cancer was reported to increase VTE risk compared with doxorubicin alone.[55] Evidence has been presented to support the association of immunomodulating agents that have antiangiogenic properties (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 (see Outpatient Prophylactic Therapy in Ambulatory Cancer Patients, page 749).[41,56–61] In addition, a meta-analysis of randomized clinical trials showed that cancer patients undergoing chemotherapy with bevacizumab had a significantly increased risk of VTE compared with those undergoing chemotherapy without this agent.[62] Other agents used in supportive cancer care (e.g., erythropoietic stimulatory agents) have also been associated with the development of VTE.[25,63] Concomitant use of erythropoietin with other therapies associated with the development of VTE (e.g., lenalidomide) may further increase risk.[59]

Results from numerous studies have identified the presence of a CVAD as a risk factor for development of an upper-extremity DVT (UEDVT),[32,64–66] although discrepancies exist in the incidence of CVAD-related DVT.[66,67] The association between catheter/device placement and the development of DVT may be the result of venous stasis and vessel injury after insertion of the CVAD,[66,68,69] or infections occurring as a result of catheter placement.[69,70] Possible reasons for the reported discrepancies in the incidence of CVAD-related DVT may include recent improvements in catheter materials and design, and the different methods of diagnosing device-related DVT used in some of the studies (i.e., clinical, which are symptomatic, vs. radiologic, which could be symptomatic or asymptomatic).[66,67]

Diagnosis and Evaluation

VTE in Cancer Patients

Clinical prediction models, such as the Wells criteria, in combination with D-dimer testing have proven useful in diagnosing VTE, with comparable results to conventional radiologic imaging strategies. However, cancer patients constituted a minority of the subjects in these studies,[71,72] and therefore whether this strategy is as safe or effective in cancer patients is unclear. Although one study using the Wells criteria and D-dimer testing to diagnose VTE noted that the performance of this strategy was comparable in patients with and without cancer, the number of cancer patients (in whom VTE had been excluded with testing) with symptomatic VTE during follow-up was 4-fold higher (2.0% vs. 0.5%; not significant because of wide confidence intervals). In addition, the number of false-positive D-dimer assays was 3-fold higher in cancer patients than in non-cancer patients,[73] and results of a large prospective study of patients with suspected DVT that had been excluded on radiologic testing showed that high D-dimer levels were present in a large percentage of patients with cancer.[74] D-dimer testing is not recommended for diagnosing VTE in cancer patients, and further investigation/validation of D-dimer testing and clinical prediction models is warranted before these strategies are incorporated into the diagnostic evaluation of VTE in cancer patients.

In addition to the imaging described below, the initial diagnostic workup of all patients with suspected VTE should undergo the following tests: comprehensive medical history and physical examination; CBC with platelet count; prothrombin time (PT); activated partial thromboplastin time (aPTT); and serum creatinine (see pages 718 and 721).

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 face, neck, or supraclavicular space; unexplained persistent cramping) are not present in all cases of acute DVT. In the prospective MASTER registry of patients with VTE, the most common presenting symptoms of DVT were extremity edema, pain, and erythema observed in 80%, 75%, and 26% of patients with DVT, respectively.[75] Diagnosis of DVT in adults with cancer should be tempered by an increased level of clinical suspicion on presentation of any clinically overt signs/symptoms that could represent an acute DVT.

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,[76] although assessment of venous compressibility is considered to be more definitive.[65,77] Other advantageous characteristics of ultrasonography include accuracy in diagnosing symptomatic DVT in femoral and popliteal veins; noninvasive methodology; the lack of need for intravenous contrast agents; ability to be performed at the bedside; and lower cost.[76,78] Two normal ultrasound examinations obtained 1 week apart have been reported to exclude progressive lower-extremity DVT,[77] although these types of studies have not been

performed in cancer patients. Disadvantages of ultrasonography include difficulties associated with imaging more central veins, such as large pelvic veins, the proximal subclavian vein, the IVC, and the SVC[79,80]; a lower sensitivity for diagnosing distal lower-extremity DVT and asymptomatic DVT[81]; limitations associated with bandages, casts, or pain; and results that are more operator-dependent.[82]

In cases of negative or indeterminate ultrasound results after repeat venous imaging, and a continued high clinical suspicion of DVT, other imaging modalities (listed in order of preference) are recommended:

- Contrast-enhanced CT (i.e., indirect CT venography) is reportedly as accurate as ultrasonography in diagnosing femoropopliteal DVT and provides accurate imaging of the large pelvic veins and IVC.[78,83] However, this method requires relatively high concentrations of contrast agent.
- MRI (magnetic resonance venography [MRV]) provides a sensitive and specific evaluation of the pelvic veins and vena cava without the need for nephrotoxic contrast agents.[78,84,85] Drawbacks to this method include higher cost, longer imaging times, and limited availability in some practice settings.[84]
- Standard invasive venography, once considered the gold standard for DVT diagnosis, has largely been replaced by less-invasive methods.[84]

Few studies of UEDVT have been performed. Although UEDVT is frequently related to the presence of a CVAD[64,65,68,86] and associated with device malfunction,[67] 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.[65] However, in one study, only 50% of isolated flow abnormalities in the upper extremity were related to the presence of DVT.[87] A CT venogram may provide a more accurate assessment in cases of isolated flow abnormalities associated with an upper extremity.[87] CT venography or MR angiography may be needed to diagnose UEDVT located in the proximal subclavian vein, brachiocephalic vein, or the SVC.[68,69] Invasive venography for detecting UEDVT should be performed through a peripheral vessel in the extremity, although vein access may be limited by edema.

The panel recommends that patients diagnosed with calf and UEDVT who have contraindications to anticoagulation therapy be reevaluated for clot progression (e.g., at 1 week for patients with calf DVT) after initial diagnosis (see page 719). Similarly, patients with CVAD-related DVT and central/proximal DVT should undergo follow-up imaging as clinically indicated (see page 720). Reassessments of contraindications to anticoagulant therapy should accompany imaging evaluations.

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

SVT

An SVT is distinct from a DVT and generally does not have the same implications for morbidity and mortality.[88,89] Nevertheless, SVT and DVT can occur simultaneously and each predisposes the patient to the other condition.[89] Few data are available on the incidence of SVT in patients with cancer; most SVTs in the lower extremities are estimated to occur in the greater saphenous vein.[88,89] Although the clinical sequelae of SVT are generally less severe than those of DVT, an extensive SVT in the saphenous vein can progress to involve the deep venous system at the saphenofemoral junction. These clots can precipitate PE. Therefore, the location and extent of SVT should be evaluated with venous ultrasound if the possibility of proximal deep vein involvement exists.[89]

SVT is diagnosed primarily based on clinical symptoms (e.g., tenderness, erythema, and/or an indurated cord associated with a superficial vein) and a negative ultrasound finding for DVT. Progression of symptoms should be accompanied by follow-up imaging. SVT is more likely than DVT to be symptomatic (e.g., associated with pain, tenderness, erythema), especially if occurring in the lower extremities. Peripheral catheter-related SVT, sometimes referred to as *infusion thrombophlebitis*, is often associated with a palpable tender cord along the course of the affected vein.[89] A key decision point in the treatment algorithm for SVT is the location of non–catheter-related SVT.

Trousseau's Syndrome

The presence of migratory thrombophlebitis in the presence of cancer should increase clinical suspicion for the presence of a relatively rare condition called *Trousseau's syndrome*. The clinical characteristics of Trousseau's syndrome can include warfarin resistance, thrombocytopenia, chronic disseminated intravascular coagulation, nonbacterial thrombotic (verrucous) endocarditis, and arterial emboli.[90,91] Effective treatment of thrombosis in Trousseau's syndrome requires the use of unfractionated or low-molecular-weight heparin or fondaparinux.

Splanchnic Vein Thrombosis

Splanchnic vein thrombosis (SPVT) refers to a relatively rare group of VTEs within the splanchnic vasculature comprising the hepatic (characteristic of Budd-Chiari syndrome), portal, mesenteric, and splenic venous segments.[92,93] Thrombotic events may occur in multiple segments (38%–50% of SPVT cases) or in isolated segments within the splanchnic vasculature, with isolated portal vein thrombosis (34%–40% of SPVT cases) being the most common among the latter.[93,94] Limited data are available to assess the relative prognosis of patients with SPVT according to the venous segment affected. In a large single-center retrospective analysis of patients with SPVT (N = 832), the 10-year survival rate was significantly decreased among patients with thrombosis in multiple segments compared with those with thrombosis in a single/isolated segment (48% vs. 68%; $P < .001$); the 10-year survival rate for the entire cohort was 60%.[93] Moreover, the 10-year survival rate was highest among patients with isolated hepatic vein thrombosis (82%), whereas the lowest survival rate (63%) was reported in those with isolated portal vein thrombosis ($P = .045$ for comparison of Kaplan-Meier survival estimates across subgroups of isolated SPVT). The investigators attributed the lower survival rate of patients with portal vein thrombosis to the relatively high incidence of malignancies present in this group; in this retrospective study, the presence of malignancy was significantly associated with decreased survival for patients with SPVT, both in univariate and multivariate analyses.[93] In a separate retrospective study in patients with extrahepatic portal vein thrombosis (N = 172), a concurrent diagnosis of mesenteric vein thrombosis was significantly predictive of decreased survival based on multivariate analysis; presence of cancer was also a significant independent predictor of mortality.[95] Several smaller retrospective studies have also reported on adverse outcomes for patients with mesenteric vein thrombosis, with a 30-day mortality rate of 20%.[96,97] Thromboses in the mesenteric vein can lead to intestinal infarction, which is frequently life-threatening.[96,97] In one study, intestinal infarction was present in 45% of patients diagnosed with mesenteric vein thrombosis, of which 19% were fatal.[94]

Various risk factors have been identified in the development of SPVT, including inherited thrombophilic states (i.e., antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden mutation, prothrombin *G20210A* mutation) and acquired risk factors, such as malignancies, myeloproliferative disorders (e.g., polycythemia vera, essential thrombocythemia), *JAK2V617F* mutation with or without overt myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria (PNH), abdominal surgery (e.g., splenectomy), pancreatitis, and cirrhosis.[94,95,98–100] In addition, the use of exogenous estrogen (e.g., oral contraceptives, hormone replacement therapy) has also been linked to SPVT.[95,98,100] Patients with SPVT may have multiple risk factors, whether inherited and/or acquired. The presence of cancer itself, especially abdominal malignancies (e.g., hepatocellular carcinoma, pancreatic carcinoma), is both a common risk factor for SPVT and a frequent cause of death in cancer patients with SPVT.[93,95,100] Several retrospective studies have reported cancer to be a significant independent predictor of mortality in patients with SPVT.[93,95–97] Moreover, among patients with cancer, the presence of SPVT has been associated with decreased survival. Portal vein thrombosis has been reported in 20% to 30% of patients with hepatocellular carcinoma at diagnosis.[101–103] In a retrospective study of patients with hepatocellular carcinoma treated at a referral center in Germany (N = 389), patients with portal vein thrombosis had significantly decreased median survival (6 months) compared with those without portal vein thrombosis (16 months); based on multivariate analysis, presence of portal vein thrombosis was a significant independent predictor of 5-year survival in this population.[102] The poor prognosis associated with SPVT in patients with hepatocellular carcinoma was shown in another retrospective study (N = 194), which also showed significantly decreased median survival in patients with

portal vein thrombosis (2.3 vs. 17.6 months in patients without; $P = .004$).[101] In a recent meta-analysis of 30 randomized controlled trials in patients with previously untreated hepatocellular carcinoma undergoing palliative treatments, the presence of portal vein thrombosis was identified as one of the independent predictors of decreased survival.[104]

Clinical manifestations of acute SPVT typically include abdominal pain, ascites, hepatomegaly, nausea, vomiting, anorexia, and diarrhea (see page 727).[100,105–110] Among patients with acute thrombosis in the mesenteric vein, intestinal infarction has been reported in 30% to 45% of patients at diagnosis.[94,96] Abdominal pain associated with mesenteric vein thrombosis has been described as mid-abdominal, colicky pain.[100] Fever, guarding, and rebound tenderness may also be present, which may indicate progression to bowel infarction.[100] Chronic SPVT may often be asymptomatic because of the formation of collateral veins,[100,105,107,111] although abdominal pain, nausea, vomiting, anorexia, lower-extremity edema, and splenomegaly have been reported with chronic presentations.[107,110] Weight loss, abdominal distension, and postprandial abdominal pain may also be associated with chronic mesenteric vein thrombosis.[111] The presence of splenomegaly and/or esophageal varices indicates portal hypertension associated with chronic SPVT, and complications may arise because of bleeding from varices.[106,107,111]

The diagnostic evaluation includes both imaging and laboratory testing (see page 727). Diagnosis is confirmed by the absence of blood flow or presence of a thrombus in the splanchnic veins based on noninvasive imaging by duplex ultrasonography, CT angiography (CTA), and/or MRV of the abdomen. Acute SPVT is associated with presenting signs or symptoms lasting 8 weeks or less, with no portal cavernoma (cavernous transformation showing a network of collaterals around the portal vein) and no signs of portal hypertension.[108] The presence of portal cavernoma on imaging indicates chronic thrombosis.[106,108,112] For suspected cases of SPVT involving the hepatic and/or portal veins, duplex ultrasonography is considered the initial choice of imaging.[98,105,106,112] CTA or MRV may be useful for evaluating vascular structure, venous patency, the presence of ascites, and potential impairment of the bowel and other adjacent organs, and for identifying complications such as bowel ischemia.[98,111,112] In cases of SPVT involving the mesenteric veins, duplex ultrasonography frequently may be limited by overlying bowel gas; for suspected mesenteric vein thrombosis, CTA should be the preferred method of diagnostic imaging.[98,100,111] Once SPVT is diagnosed, evaluating for thrombophilia or testing for PNH or the *JAK2* gene mutation may be considered. PNH is a rare acquired hematopoietic disorder that results in chronic hemolysis, and has been associated with a high propensity for venous thrombosis, particularly in the splanchnic vasculature.[113,114] PNH is an important acquired risk factor for SPVT[98,100]; in a recent post hoc analysis (N = 77) from a study of patients with Budd-Chiari syndrome, patients who had underlying PNH more frequently presented with additional SPVT (i.e., portal, mesenteric, or splenic vein thrombosis) at baseline than those without PNH (47% vs. 10%, respectively; $P = .002$).[115] The *JAK2V617F* mutation is detected in a high proportion of patients with polycythemia vera, essential thrombocythemia, and primary myelofibrosis, and is now part of both the diagnostic and the prognostic assessment of these myeloproliferative disorders.[116–119] The presence of myeloproliferative disorders, or the *JAK2V617F* mutation with or without myeloproliferative disorders, is the most common acquired risk factor for SPVT.[98] In the absence of overt myeloproliferative disorders, *JAK2V617F* was detected in 20% to 40% of patients with SPVT.[98,120–122] Mutations in exon 12 of *JAK2* may also be associated with SPVT in patients without *JAK2V617F*.[123] In patients with a confirmed diagnosis of SPVT, testing for *JAK2* mutations may be warranted to monitor for potential development of overt myeloproliferative disease.

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., unexplained shortness of breath, chest pain, particularly pleuritic chest pain, tachycardia, apprehension, tachypnea, syncope, and hypoxia) are not present in all cases of acute PE. The clinical presentation of PE can range from stable hemodynamics to cardiogenic shock.[124] In the prospective MASTER registry, the most common presenting symptoms of PE were dyspnea, pain, and tachypnea, which were present in 85%, 40%, and 29% of patients with PE, respectively.[75]

Radiographic evidence of DVT is found in 50% to 70% of patients presenting with symptomatic PE and vice versa.[75,125,126] Asymptomatic patients with incidental radiographic findings of PE should be treated similarly to those with symptomatic PE, because many have subtle clinical symptoms of active disease on further evaluation.[127] They should undergo additional workup and imaging (e.g., CTA) to evaluate for PE (see page 721).

Neither a chest radiograph nor an EKG is sensitive or specific enough to diagnose PE when suspected. However, a chest radiograph facilitates the diagnosis of comorbidities and conditions with clinically similar presentations and is useful in interpreting a ventilation-perfusion (V-Q) lung scan.[128] The EKG provides information about existing cardiac disease and PE-related changes. Furthermore, EKG patterns characteristic of right ventricular strain have been associated with PE,[129] and inverted T waves in precordial leads may be evident in cases of massive PE.[130]

The panel recommends CTA, which allows for indirect evaluation of pulmonary vessels, as the preferred imaging technique for the initial diagnosis of PE in most patients (see page 721). Advantages of this method include accurate imaging of mediastinal and parenchymal structures; accurate visualization of emboli in many regions of the pulmonary vasculature; capability of being performed in conjunction with indirect CT venography, which can detect DVT[78,131] (because the most common cause of PE is DVT in the lower extremities or pelvis[132]); and the ability to detect signs of right ventricular enlargement, which can be used to assess the patient's risk for adverse clinical outcomes.[133] Disadvantages of CTA include the associated radiation exposure and the need for large amounts of intravenous contrast, particularly when CTA is followed by indirect CT venography.[78]

Alternative imaging modalities used for diagnosing PE include a V-Q lung scan and conventional pulmonary angiography. A V-Q scan is associated with less fetal radiation exposure than CTA, and is therefore useful in pregnant patients and those with renal insufficiency or untreatable contrast allergies in whom intravenous contrast is not feasible. It is also less invasive than conventional pulmonary angiography. A normal scan result essentially excludes PE.[134] In a recent noninferiority study in which 1417 patients determined to have a high risk of PE according to the Wells criteria were randomized to undergo CTA or V-Q scanning, CTA identified significantly more PEs than V-Q scans (19.2% vs. 14.2%; 95% CI, 1.1%–8.9%).[134] Elderly patients are more likely than younger patients to be diagnosed with an intermediate-probability V-Q scan result.[135] Both intermediate- and low-probability V-Q scan results lack diagnostic efficacy and should be considered indeterminate. Further diagnostic testing should be performed if indicated clinically. When a PE is clinically suspected, a high-probability V-Q scan is diagnostic. Conventional pulmonary angiography (direct pulmonary angiography), often considered to be the gold standard for PE diagnosis, is infrequently used because of its invasive nature. Rarely, this method is combined with catheter-directed thrombectomy or thrombolysis. These measures should be planned before and executed simultaneously with conventional pulmonary angiography.

Fatality caused by PE primarily occurs through right ventricular heart failure and cardiogenic shock.[124] Because the 3-month mortality rate of patients with PE has been reported to be 15%, outpatient management should be limited to individuals at low risk of adverse outcomes.[136] The panel recommends that patients with PE be risk-stratified.[137,138] CTA or echocardiography can be used to assess these patients for right ventricular enlargement/dysfunction, which is associated with an increased risk for adverse clinical outcomes.[124,133,136,139–142] Elevated serum troponin levels, which are released because of endomyocardial damage, have also been associated with adverse clinical outcomes,[124,139,143,144] as has the presence of residual DVT on lower-extremity duplex imaging.[145] A recent study showed that, compared with using individual tests alone, combining the results from at least 2 of the previously mentioned tests (i.e., serum troponin measurement, echocardiography for detecting right ventricular dysfunction, lower-extremity ultrasonography for detecting DVT) improved the specificity and positive predictive value in identifying patients at high risk for PE-related mortality.[137] A clinical risk assessment tool, the Pulmonary Embolism Severity Index (PESI), has also been used to assess the advisability of outpatient management and intensity of initial follow-up and treatment. The PESI score is a validated patient assessment rule that includes age, sex, a history of heart or lung disease, a history of cancer, and physiologic signs associated with PE that can be used to deter-

mine a patient's risk for an adverse outcome associated with PE.[146,147] Patients with low PESI scores (≤ 85 points) are considered to be at low risk for an adverse outcome, whereas those with high PESI scores (≥ 86 points) are at high risk. Because the subject populations in the original PESI score derivation/validation study and subsequent studies only included a small number of patients with cancer, further validation of this score is warranted in this population. The panel recommends that all cancer patients with PE be risk stratified using a combination of imaging modalities (CTA or echocardiography with or without duplex ultrasonography) plus serum troponin measurement.[137,138] The PESI score can be included as an adjunctive risk assessment tool but should not be used in isolation until further validation is conducted in cancer patients.

Anticoagulation in Cancer Patients: Contraindications and Risks

Contraindications to Anticoagulation

Contraindications to anticoagulation, possibly of a temporal nature, that place patients at an increased risk for bleeding may include clinically significant active or chronic bleeding; recent central nervous system bleeding or intracranial or spinal lesions at high risk for bleeding; recent surgery with a high associated bleeding risk; spinal anesthesia/lumbar puncture; patients at a high risk for falls and/or head trauma; thrombocytopenia or platelet dysfunction; and a systemic coagulopathy, as evidenced by a prolonged PT or aPTT (see page 730). The panel recommends frequent reevaluation of these contraindications and the risks and benefits of anticoagulation therapy for any cancer patient considered to be at increased risk for bleeding to facilitate the implementation of this 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 for 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.[148–151] Unfractionated heparin (UFH) should also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture.[152] Other factors, such as a patient's risk of falling, should also be considered before anticoagulation therapy is ordered.

A prolonged aPTT is not considered a contraindication to anticoagulation therapy in patients with a lupus inhibitor or lupus anticoagulant (e.g., antiphospholipid syndrome). Antiphospholipid antibodies prolong the aPTT through interfering with the interaction between coagulation factors (in the patient plasma sample) and the phospholipids provided in the aPTT test reagent. Antiphospholipid antibodies have been associated with an increased risk of VTE and arterial thromboembolism, and with adverse pregnancy outcomes.[153–155] Any patient who has experienced a thrombotic event and fulfills diagnostic criteria for antiphospholipid syndrome should be considered for indefinite anticoagulation therapy.[154]

Risks Associated With Anticoagulation Therapy

The use of anticoagulants in cancer patients is complicated by the fact that these patients have higher risks of both recurrent VTE and bleeding.[30,156,157] In one prospective follow-up study of patients undergoing anticoagulation therapy for VTE, the 12-month cumulative incidence of major bleeding was 12.4% and 4.9% in patients with and without cancer, respectively (hazard ratio [HR], 2.2; 95% CI, 1.2–4.1).[30] In this study, one-third of all major bleeding cases occurred during the initial 5 to 10 days of heparinization, and the risk of bleeding increased with the extent of cancer. In contrast to patients without cancer, those with cancer remain at increased risk for bleeding during vitamin K antagonist therapy regardless of International Normalized Ratio (INR) level.[30,156,157] These findings suggest that factors other than the intensity of anticoagulation (e.g., thrombocytopenia, organ or vascular invasion by tumors) are responsible for increased bleeding in cancer patients. Subsequent randomized controlled studies of LMWHs and vitamin K antagonists in the chronic treatment of VTE in cancer patients have shown that LMWH is associated with a similar incidence of bleeding events, including major bleeding[158–160]; however, in one study, fatal bleeding within the 3-month treatment period was reported in 8% of patients receiving vitamin K antagonists compared with none receiving LMWH.[160] Other risks associated with chronic use of anticoagulants include osteoporosis and heparin-induced thrombocytopenia

(HIT) for patients receiving heparins (see Related Issues in VTE Prophylaxis and Treatment, page 760), and drug and food interactions for patients receiving oral anticoagulants. For example, in patients who underwent chronic anticoagulant therapy for 3 to 24 months with an oral anticoagulant or enoxaparin, decreases in bone mineral density of 1.8% and 3.1% at 1-year follow-up, and 2.6% and 4.8% at 2-year follow-up, respectively, were seen.[161]

Warfarin has a very narrow therapeutic window, and its activity is known to be affected by the administration of many other drugs. For example, several 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.[162,163] Furthermore, certain chemotherapeutic agents such as the fluoropyrimidines (e.g., 5-fluorouracil and capecitabine) are known to increase the INR in patients undergoing warfarin anticoagulation,[164,165] and drug interactions between warfarin and certain selective estrogen-receptor modulators (e.g., tamoxifen and raloxifene) have also been reported.[166] Dietary intake of vitamin K and certain dietary supplements can also influence the effects of warfarin.[167,168] Finally, acetaminophen, which is found in many medications, can increase the therapeutic effects of warfarin when taken in daily doses exceeding 2 g.[169]

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.[170,171] 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 these therapies is strong.[171–173] Clinical evidence for the safety and efficacy of anticoagulation therapy in cancer patients is described later (see VTE Prophylaxis, page 748, and VTE Treatment, page 752). It is the directive of NCCN that all hospitalized adult patients with cancer receive anticoagulation therapy in the absence of contraindications (category 1).

Anticoagulants

Anticoagulation agents used in the prophylaxis and/or treatment of VTE that are listed and described according to guideline recommendations (see Inpatient/Outpatient Prophylactic Anticoagulation Treatment, page 730; Therapeutic Anticoagulation Treatment for VTE, page 731; and Therapeutic Options for HIT, page 726). FDA indications and NCCN recommendations for use of each of these therapies are listed in the NCCN Drugs & Biologics Compendium (NCCN Compendium) for Venous Thromboembolic Disease (to view the NCCN Compendium, visit the NCCN Web site at www.NCCN.org). The panel recommends that agent selection be based on criteria such as the presence of renal insufficiency, FDA approval, cost, ease of administration, need for therapeutic monitoring, and ease of reversibility. Suggested dosing schedules included in the NCCN Guideline were established according to 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.[172,173]

Low-Molecular-Weight Heparins: LMWHs such as dalteparin, enoxaparin, and tinzaparin are attractive agents for VTE treatment and prevention because they facilitate outpatient treatment and eliminate the need for therapeutic monitoring in most patients. Although these 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. Results from a randomized clinical study comparing tinzaparin with dalteparin in the treatment of DVT and PE in 505 patients, including 113 with active cancer, support the premise that these 2 drugs are equivalent in efficacy (preventing recurrence of VTE) and safety,[174] although the results of studies in patients with renal insufficiency suggest that not all LMWHs behave identically in this patient

population (see later discussion). Enoxaparin[149] is approved by the FDA for both prophylaxis and immediate treatment of VTE; tinzaparin[148] is currently approved only for immediate VTE treatment; and dalteparin[151] 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 the results of clinical studies and panel consensus (see page 731).[159,174–178] Extended or chronic anticoagulation therapy with an LMWH may require dosage reduction after an initial period. For example, in the CLOT study (Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer), the dalteparin dosing was lowered from 200 to 150 units/kg every day after 1 month.[159] In addition, the European Society for Medical Oncology (ESMO) clinical recommendations for the management of VTE in cancer patients specifies using 75% to 80% of the initial dose of LMWH for extended anticoagulation therapy.[179] Only limited evidence exists concerning the safety and efficacy of LMWHs in special populations, such as patients with renal insufficiency, obese patients (body mass index > 30 kg/m^2), patients weighing less than 50 kg, elderly patients (≥ 70 years of age), and patients with cancer.[180–182]

Among the 3 LMWHs, specific dosing recommendations for patients with severe renal insufficiency (creatinine clearance [C_{cr}] < 30 mL/min) are available for enoxaparin.[149,183] For patients with C_{cr} less than 30 mL/min, manufacturer recommendations specify 30 mg of enoxaparin subcutaneously daily for VTE prophylaxis, and 1 mg/kg subcutaneously every 24 hours for VTE treatment. These recommendations are supported by results of a meta-analysis showing that enoxaparin is associated with a 2- to 3-fold increase in risk of bleeding when administered in standard, unadjusted therapeutic doses to patients with severe renal insufficiency compared with those without severe renal insufficiency.[184] 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 dose reductions for patients with C_{cr} values less than 50 mL/min.[185] Furthermore, some evidence supports downward dose adjustments of enoxaparin in the management of patients with C_{cr} of 30 to 60 mL/min.[186]

Some data are available with respect to the safety of dalteparin and tinzaparin in patients with renal insufficiency. In a small study of patients treated with dalteparin (N = 22), mean anti-Xa activity was similar between patients with renal impairment (mean C_{cr}, 26 mL/min; range, 16–38) and those with normal renal function (C_{cr} > 80 mL/min).[187] In a more recent study of prophylactic dalteparin in critically ill patients (N = 138 evaluable) with severe renal impairment (C_{cr} < 30 mL/min), no bioaccumulation was detected after a median of 7 days of dalteparin (5000 IU daily), and treatment was not associated with excessive anticoagulation; peak anti-Xa levels were between 0.29 and 0.34 IU/mL.[188] For cancer patients with C_{cr} less than 30 mL/min receiving dalteparin for extended treatment of acute VTE, the manufacturer recommends monitoring of anti-Xa levels to achieve a target range of 0.5 to 1.5 IU/mL.[151]

In addition, tinzaparin, unlike enoxaparin, did not accumulate when used as VTE prophylaxis for 8 days in elderly patients with a mean C_{cr} of 35 mL/min[189] or in elderly patients (> 70 years of age) with renal insufficiency (but C_{cr} > 20 mL/min) receiving therapeutic doses of tinzaparin (175 IU/kg daily) for 10 days.[190,191] However, results from a randomized clinical trial of elderly patients with a C_{Cr} less than 60 mL/min undergoing initial treatment for VTE showed that those receiving tinzaparin had a substantially higher mortality rate compared with those receiving UFH (11.2% vs. 6.3%; P = .049).[192] Although the rates of bleeding and recurrent VTE did not differ between the arms, the trial was terminated early, and the panel recommends that tinzaparin be avoided in patients aged 70 years or older with renal insufficiency (see page 730).

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.[149] The panel also recognizes current evidence suggesting caution should be used when administering LMWHs to patients with C_{cr} less than 50 mL/min. Additional studies are needed to determine the safety of LMWH in patients with compromised renal function, including patients with cancer.

Concerns also exist with respect to maintaining and monitoring therapeutic concentrations of anti-

coagulants 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.[193] Hospitalization of morbidly obese cancer patients with administration of UFH should be considered. The panel suggests that each institution prepare a LMWH dosing algorithm tailored for obese patients. Because only limited data are available for the use of LMWHs in patients weighing less than 50 kg,[148,149,151] the panel also recommends caution when using these agents in patients with low body weight and those who are elderly. LMWHs are contraindicated in patients with HIT, and should only be used with caution in patients with a history of HIT. In this situation, a direct thrombin inhibitor (DTI) or fondaparinux represents a safer alternative (see Related Issues in VTE Prophylaxis and Treatment, page 760). Later sections summarize the clinical evidence for the safety and efficacy of LMWHs in cancer patients (see VTE Prophylaxis, page 748, and VTE Treatment, page 752).

Fondaparinux: Fondaparinux is the only specific factor Xa inhibitor approved by the FDA for the prophylaxis and treatment of VTE.[150] Advantages of fondaparinux in the treatment of VTE include specific neutralization of factor Xa, elimination of the need to monitor anticoagulant response in most patients, and the lack of cross-reactivity with the antibody associated with HIT.[150,194–196] However, the use of fondaparinux in patient populations with renal insufficiency, obesity, or HIT has not been well defined,[182,196] although some evidence shows that it is safe and effective for VTE prophylaxis in older patients with a broad range of body weights.[197] Pharmacologic characteristics of fondaparinux include renal elimination and a very long half-life of 17 to 21 hours.[150] Prescribing information provided by the manufacturer specifies that fondaparinux is contraindicated in patients with severe renal insufficiency (C_{cr} < 30 mL/min) and for treating thromboprophylaxis in patients weighing less than 50 kg undergoing orthopedic or abdominal surgery.[150] It should be used with caution in elderly patients[197] and individuals with moderate renal insufficiency (C_{cr} < 50 mL/min).[150] The panel recommends against its use in patients with severe renal insufficiency and advises caution when using it in all patients weighing less than 50 kg, patients with renal dysfunction (C_{cr}, 30–50 mL/min), and elderly patients (> 75 years of age).

UFH: UFH is generally administered subcutaneously for VTE prophylaxis (low-dose heparin) and intravenously for VTE treatment.[198] Low-dose UFH (5000 units) administered 3 times daily (every 8 hours) was shown to be more effective than low-dose UFH administered twice daily in preventing DVT in general surgery patients,[199] and is the regimen the panel recommends for VTE prophylaxis in cancer patients. However, a meta-analysis of clinical trials conducted in general medical patients noted no difference in the overall rate of VTE based on the dosing of prophylactic UFH (5000 units, twice daily vs. 3 times daily), although a decrease was seen in the combined end point of proximal DVT and PE (P = .05), and the risk for major bleeding was significantly higher when UFH was administered 3 times daily (P < .001).[172,200]

Initial dosing of UFH in the treatment of VTE is weight-based, with a recommended regimen of 80 units/kg bolus followed by 18 units/kg per hour infusion.[181] The safety and efficacy of fixed-dose, unmonitored, subcutaneous UFHs were reported to be comparable to LMWHs for treating patients with acute VTE,[201] but further investigation is needed before this regimen can be used routinely in cancer patients. Patients receiving intravenous UFH must initially be hospitalized and monitored for anticoagulant response. The panel recommends UFH as the preferred agent in patients with C_{cr} less than 30 mL/min, because the liver is a main site of heparin biotransformation.[152,194] Some exceptions include patients with severe renal dysfunction but without intravenous access, and those with a new diagnosis of VTE despite therapeutic doses of UFH. UFH is contraindicated in patients with HIT and should only be used with extreme caution in patients with a history of HIT. In this situation, a DTI or fondaparinux is a better alternative (see Related Issues in VTE Prophylaxis and Treatment, page 760).

Warfarin: Warfarin is an option for long-term treatment of VTE in cancer patients. If warfarin is to be used for chronic therapy, it should be administered concomitantly with UFH, LMWH, or fondaparinux for at least 5 days and until an INR of 2 or more is achieved before the parenteral anticoagulant agent is discontinued. When treating patients with HIT, warfarin should not be initiated until the platelet count has recovered, and then it should be overlapped with a DTI for at least 5 days and until the INR is 2 or

more (see Related Issues in VTE Prophylaxis and Treatment, page 760). During the transition to warfarin monotherapy, the INR should be measured at least twice weekly and then at least once every week when the patient is receiving warfarin monotherapy. Warfarin can be safely administered to patients with renal insufficiency, although response may be potentiated in patients with hepatic insufficiency.[202]

Aspirin: Aspirin (81–325 mg daily) is an option for VTE prophylaxis in only a select group of patients with multiple myeloma who have one or no individual or multiple myeloma risk factors (Table 1). Aspirin is not considered to be effective VTE prophylaxis in other settings. For example, in the Women's Health study, a 10-year study of healthy women randomly assigned to aspirin or placebo on alternate days, no significant differences in the incidence of VTE were observed between the arms.[203]

DTIs: DTIs are discussed in a later section (see pages 723 and 724).

Mechanical Devices

Intermittent Pneumatic Venous Compression Device: One of the main advantages of an intermittent pneumatic venous compression (IPC) device is the absence of an associated bleeding risk. However, disadvantages include the potential for interference with ambulation and the need to keep the devices in place nearly continuously.[172] Graduated compression stockings can be used in conjunction with an IPC device as a method of mechanical prophylaxis.

Vena Cava Filters: Vena cava filters are indicated for prevention of PE in patients who cannot be anticoagulated because of a contraindication or complication.[204–208] However, placement of an IVC filter does not prevent DVT and has been associated with an increased risk of recurrent DVT.[204,209,210] Only one randomized controlled trial has compared the efficacy and safety of IVC filters in conjunction with anticoagulation versus anticoagulant therapy alone in the treatment of acute VTE. Unfortunately, this pivotal trial did not test the efficacy of IVC filters in the usual clinical scenario in which they are used: in patients without concomitant anticoagulation.[204,209]

Both retrievable ("optional") and permanent IVC filters are available; however, the period for recovery of a retrievable filter is limited.[211,212] 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.[213] No significant differences in protection or complication rates were observed with the 2 types of filters, although mean follow-up time was limited to 11.5 months in this study. A recent case series of patients who received a Bard G2 or Recovery filters noted filter strut fracture in up to 25% of recipients after a mean follow-up of 24 and 50 months, respectively.[214] Whether the frequency of this complication is device-specific or a property of all filters remains unclear. Until further data are available, this experience emphasizes the importance of placing filters only in patients in whom the benefits outweigh the risks, and of retrieving filters whenever possible.

VTE Prophylaxis

Prophylactic Anticoagulation Therapy

Inpatient Prophylactic Therapy: Hospitalized patients with cancer are at high risk for VTE.[215] The panel recommends prophylactic anticoagulation therapy for all inpatients diagnosed with active cancer (or in whom cancer is clinically suspected) who do not have a contraindication to this therapy (category 1; see pages 716 and 730). 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 in cancer inpatients are listed in the algorithm (see page 730). The LMWHs, fondaparinux, and subcutaneous UFH (5000 units, 3 times daily) are category 1 options for inpatient prophylactic therapy. Anticoagulation therapy should be administered throughout hospitalization. Adult inpatients with cancer should undergo the following tests before initiation of thromboprophylaxis: comprehensive medical history and physical examination, CBC with platelet count, PT, aPTT, and serum creatinine (see page 716).

Studies comparing different anticoagulant regimens for VTE prevention in cancer patients have not clearly identified a particular regimen with superior efficacy. In a randomized multicenter clinical trial, no difference in VTE and bleeding rates were seen for cancer patients receiving perioperative enoxaparin (40 mg) once daily versus low-dose UFH 3 times daily to prevent VTE after major elective abdominal or pelvic surgery.[216] Furthermore, results from a meta-

Table 1 Risk Assessment for Venous Thromboembolic Disease in Patients With Multiple Myeloma

Risk Factors	Recommended Action
Individual risk factors	*No Risk Factor or Only One Individual/Myeloma Risk Factor:*
Obesity (body mass index ≥ 30 kg/m^2)	Aspirin, 81-325 mg, once daily
Prior venous thromboembolic disease	*≥ 2 Individual/Myeloma Risk Factors:*
Central venous access device or pacemaker	Low-molecular-weight heparin (equivalent to enoxaparin, 40 mg, once daily); or
Associated disease:	Full-dose warfarin (target INR 2-3)
• Cardiac disease	
• Chronic renal disease	
• Diabetes	
• Acute infection	
• Immobilization	
Surgery:	
• General surgery	
• Any anesthesia	
• Trauma	
Use of erythropoietin	
Blood clotting disorders	
Myeloma-Related Risk Factors	
• Diagnosis of myeloma, per se	
• Hyperviscosity	
Myeloma Therapy	*Therapies as Described in the Left Column:*
Thalidomide or lenalidomide in combination with:	Low-molecular-weight heparin (equivalent to enoxaparin, 40 mg, once daily); or
• High-dose dexamethasone (≥ 480 mg/mo)	Full-dose warfarin (target INR 2-3)
• Doxorubicin	
• Multiagent chemotherapy	

Abbreviation: INR, International Normalized Ratio.
Adapted with permission from Macmillan Publishers Ltd: Leukemia. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414–423. ©2008.

analysis of randomized clinical studies of general surgery patients found LMWHs to be as safe and effective as UFH in preventing VTE.[217] However, results from a nonrandomized, historically controlled study comparing the effectiveness of the LMWH dalteparin (5000 units, once daily) to low-dose UFH (5000 units, 3 times daily) 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.[218] More recently, a meta-analysis comparing outcomes of perioperative VTE prophylaxis with LMWH versus UFH in cancer patients showed no difference in mortality rates, suspected DVT, PE, or bleeding events.[219]

For prevention of CVAD-associated VTE, randomized controlled studies have not established the efficacy of prophylactic doses of LMWH dose or low-dose warfarin (1 mg daily).[220–222] A recent randomized trial showed that dose-adjusted warfarin (INR, 1.5–2.0) was significantly more effective than fixed-dose warfarin (1 mg daily) in preventing CVAD-associated VTE at a cost of a trend toward more bleeding; however, neither dose-adjusted nor fixed-dose warfarin showed statistically significant reductions in VTE compared with placebo.[223] These data suggest that therapeutic or near therapeutic doses of anticoagulation are probably necessary to successfully prevent CVAD-associated VTE. Until additional data are available, the panel does not recommend VTE prophylaxis for cancer patients with a CVAD.

Outpatient Prophylactic Therapy in Ambulatory Cancer Patients: Certain groups of cancer patients

are known to remain at risk for VTE after discharge from the hospital. The risk of VTE is sufficiently high in some surgical and medical oncology patients that VTE prophylaxis should be considered in the outpatient setting (see pages 717 and 730). Cancer patients undergoing abdominal or pelvic surgery with additional VTE risk factors should be considered for outpatient prophylaxis.[224] Features that place surgical oncology patients at higher risk for VTE include a previous episode of VTE, anesthesia times longer than 2 hours, advanced-stage disease, perioperative bed rest of 4 or more days, and patient age of 60 years or older.[14] Extended prophylaxis to 4 weeks postsurgery was associated with a greater than 50% reduction in venographic VTE in patients undergoing major abdominal surgery.[225,226] Because thromboembolic postoperative complications greatly exceeded hemorrhagic complications as a cause of death in the @RISTOS observational cohort study of cancer surgery patients,[14] extended (up to 4 weeks) VTE prophylaxis is recommended for high-risk cancer surgery patients.

Despite a lack of consistent evidence supporting extended outpatient prophylaxis in most populations of ambulatory medical oncology patients,[227] this practice is recommended for patients with multiple myeloma receiving highly thrombogenic combination chemotherapy regimens based on limited data. Immunomodulating agents with antiangiogenic properties, such as thalidomide or lenalidomide, have been associated with high VTE rates in patients with multiple myeloma in the absence of prophylaxis, although the reported rates of VTE vary widely across studies.[41,56,57,60,227,228] It appears that several factors contribute to thrombosis associated with thalidomide or its derivatives,[228] and VTE rates are especially high when thalidomide or lenalidomide is combined with high-dose dexamethasone (≥ 480 mg/month), or doxorubicin or multiagent chemotherapy regimens.[41,56,59–61] Package inserts for thalidomide and lenalidomide include black-box warnings regarding the VTE risks associated with these agents.[229,230] For patients with multiple myeloma, the panel recommends a prophylaxis strategy based on a risk assessment model published by Palumbo et al.[41] VTE prophylaxis with either LMWH (e.g., enoxaparin 40 mg/d) or dose-adjusted warfarin (INR 2–3) is recommended for patients with multiple myeloma who are receiving lenalidomide- or thalidomide-based combination regimens associated with a thrombotic risk or in patients with 2 or more individual or disease-related risk factors (see Table 1). Aspirin prophylaxis (81–325 mg/d) is an option for patients with multiple myeloma receiving thalidomide or lenalidomide with one or no individual or multiple myeloma risk factors.

In a recent open-label, multicenter, randomized, phase III trial in patients with previously untreated multiple myeloma (N = 667) receiving thalidomide-containing regimens, both aspirin (100 mg/d) and fixed-dose warfarin (1.25 mg/d; dose adjustment allowed to maintain INR < 3) were similarly effective in reducing thromboembolic events compared with LMWH (enoxaparin, 40 mg/d).[231] The primary end point was a composite measure, including symptomatic DVT, PE, arterial thrombosis, acute cardiovascular events, or sudden otherwise unexplained death, during the first 6 months from randomization. The incidence of the composite end point was 6.4%, 8.2%, and 5% in the aspirin, warfarin, and LMWH groups, respectively.[231] The absolute risk for the composite end point was not statistically different when comparing aspirin with LMWH (absolute difference +1.3%; $P = .544$) or when comparing warfarin with LMWH (absolute difference +3.2%; $P = .183$). Although not statistically significant, LMWH was associated with trends for decreased risks for grades 3 and 4 thromboembolic events and major bleeding events compared with aspirin. However, LMWH was associated with a significantly decreased risk for grades 3 and 4 thromboembolic events compared with warfarin (absolute difference +5% for warfarin vs. LMWH; $P = .024$). Moreover, among the subgroup of patients aged 65 years or older undergoing combination therapy with bortezomib, melphalan, prednisone, and thalidomide, LMWH significantly reduced the risk for the composite end point compared with warfarin (absolute difference +11.3 for warfarin vs. LMWH; $P = .006$).[231] This study was conducted in patients with myeloma who were at "standard risk" for thromboembolism and had no clinical indication for anticoagulation or antiplatelet therapy.

In light of published data from the phase III randomized trial, the panel recommends prophylactic aspirin or LMWH in patients with multiple myeloma receiving thalidomide (excluding high-risk combinations) who have no other risk factors for VTE.

With respect to other ambulatory cancer outpatients, these NCCN Guidelines include the option

of prophylaxis in individuals considered to be at risk of VTE based on an assessment of VTE risk factors (see page 729). Recent data from a randomized, placebo-controlled, double-blind trial of patients with advanced cancer undergoing treatment with chemotherapy (PROTECHT trial) showed a statistically significant decrease in thromboembolic events (composite end point of venous and arterial) in the group receiving prophylactic LMWH (i.e., nadroparin) compared with those receiving placebo.[232] Furthermore, in the randomized CONKO-004 trial, the symptomatic VTE rate in patients with pancreatic cancer undergoing chemotherapy was significantly reduced at 3 and 12 months when enoxaparin was administered as VTE prophylaxis (1 mg/kg daily for 3 months followed by 40 mg/d for 3 months) compared with no LMWH.[233]

Khorana et al.[24] derived a VTE risk score for ambulatory medical oncology patients undergoing outpatient chemotherapy that was recently independently validated.[45] Patients designated as being at high risk for VTE based on these models could be considered for outpatient VTE prophylaxis on an individual basis. However, thromboprophylaxis in most cancer outpatients undergoing chemotherapy is controversial, and its broader application using either the Khorana or the Vienna risk assessment model should await the results of randomized controlled trials evaluating the efficacy of risk-adjusted thromboprophylaxis based on these models.[234]

Mechanical Prophylaxis

IPC devices and graduated compression stockings are mechanical prophylaxis options that are principally used in patients with contraindications to pharmacologic prophylaxis or in conjunction with pharmacologic agents in patients at very high risk for VTE. Mechanical prophylaxis should not be used in patients with arterial insufficiency or open wounds, or on an extremity with an acute DVT. Whenever mechanical prophylaxis is used, steps should be taken to ensure its proper use and continuous application.

IPC devices have been less well studied than anticoagulation therapy in VTE prevention.[172] Most of the data on the effectiveness of mechanical prophylaxis are from surgical populations. For example, in a study comparing the VTE rate in gynecologic oncology surgery patients receiving either low-dose heparin 3 times daily (starting with the day before surgery and continuing for ≥ 7 days after surgery) or intermittent pneumatic calf compression, no difference was seen between the modalities.[235] A retrospective evaluation of high-risk colorectal surgery patients who had received mechanical prophylaxis without anticoagulant therapy indicated that IPC devices were effective in preventing postoperative VTE.[236] However, results from a retrospective study of 839 patients over a 2-year period who had undergone abdominal surgery for gynecologic cancers and received pneumatic compression and early ambulation for VTE prophylaxis found that the incidence of PE in cancer patients (4.1%) exceeded by 14-fold the incidence of PE in patients with benign disease (0.3%).[224] Therefore, IPC devices should only be used alone for VTE prophylaxis in patients in whom anticoagulant prophylaxis is contraindicated.

Graduated compression stockings have been shown to significantly reduce VTE compared with no prophylaxis, and provide even greater protection when combined with other preventive therapies.[237] 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 patients undergoing hip surgery found that graduated compression stockings did not provide significant additive protection against VTE in patients receiving fondaparinux, 2.5 mg daily for 5 to 9 days, suggesting that graduated compression stockings may not have significant clinical benefits in patients able to receive more potent forms of VTE prophylaxis.[238] Similarly, recent results from the CLOTS1 trial, which randomly assigned patients within 1 week of stroke to routine care with or without graduated compression stockings, found that graduated compression stockings did not reduce the incidence of DVT in these patients and was associated with a 4-fold increase in the frequency of skin ulcers and necrosis.[239] However, the patient group studied in the CLOTS1 trial differs considerably from that described in these NCCN Guidelines. Furthermore, the long delay in the institution of prophylaxis and the use of non-customized stockings suggests that results may have been more positive in this study if evidence-based application of graduated compression stockings had been used. Therefore, further investigation of these findings is warranted.

Until data become available, graduated compression stockings should not be relied on as the sole method of VTE prophylaxis in cancer patients.

VTE Treatment

After VTE is diagnosed, the panel recommends beginning immediate treatment (at least 5–7 days) with either weight-based UFH (intravenous), LMWH, or, in some cases, fondaparinux in cancer patients without contraindications to anticoagulation (see page 731). Because 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 this exist. If warfarin is to be used for chronic therapy, a short-term, transition phase of at least 5 days should occur, 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 with either an LMWH or warfarin for a minimum of 3 to 6 months, whereas patients with PE should be treated for at least 6 to 12 months.[173,240] LMWH as monotherapy (without warfarin) is recommended for the first 6 months of chronic treatment of proximal DVT or PE, and for prevention of recurrent VTE in patients with advanced or metastatic cancer who do not have contraindications to anticoagulation (category 1). However, issues such as patient preference and cost should also be considered in this decision. Anticoagulation for an indefinite duration should be considered in patients with active cancer or persistent risk factors. Because the chronic treatment of VTE with LMWHs has not been evaluated in clinical trials of cancer patients for durations longer than 6 months, decisions to continue LMWH beyond this time frame or to switch to warfarin therapy for patients requiring longer durations of anticoagulation therapy should be based on clinical judgment.

IVC filter placement should be strongly considered for patients with acute proximal lower-extremity DVT or PE who have contraindications to anticoagulation.[240] An IVC filter should also be considered in patients with PE while on adequate anticoagulation for DVT or PE; those who are nonadherent 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 thromboembolic pulmonary hypertension (see page 735). The decision whether to place a permanent or retrievable IVC filter should be based on the anticipated duration of need. When a retrievable filter is placed, patients must be followed up closely by their physicians so that the device can be removed in a timely fashion when it is no longer needed.

Improvements in technology and an increased number of available thrombolytic agents have increased the use of thrombolytic therapy for DVT. In the past, thrombolytic agents were delivered systemically through an intravenous catheter, which likely reduced the efficacy of the therapy and increased the likelihood of bleeding complications. Nevertheless, thrombolysis was associated with increased rates of complete clot lysis and a trend toward fewer postthrombotic complications compared with anticoagulation alone.[241] In recent years, catheter-directed delivery of thrombolytic agents directly into the substance of the clot has allowed more localized targeting of thrombolytic agents and the use of catheter-based thrombectomy devices to accelerate clot removal. Catheter-directed thrombolysis (CDT) with or without mechanical thrombectomy is associated with significantly higher rates of complete clot lysis than conventional anticoagulation.[242] Currently, 2 large randomized controlled trials are testing the hypothesis that catheter-directed pharmacomechanical thrombolysis is associated with improved postthrombotic outcomes. Early results from an open-label randomized controlled trial comparing CDT added to anticoagulation versus anticoagulation alone in patients with acute iliofemoral DVT (N = 103) reported a higher rate of iliofemoral patency at 6 months with the addition of CDT (64% vs. 36% with anticoagulation alone).[243] Further results from long-term follow-up are awaited from this study. Retrospective patient series have shown that cancer patients can benefit from catheter-directed pharmacomechanical thrombolysis.[244] The panel believes that CDT and thrombectomy should be considered a therapeutic option for select patients with large symptomatic extremity DVT, particularly in the absence of a response to conventional anticoagulation.[240] Thrombolytic agents and thrombectomy devices should be selected based on local expertise and experience. Broader use of CDT awaits the outcome of currently active clinical trials.

Treatment of patients with an incidental VTE after radiographic detection should be the same as for those with symptomatic VTE.

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 the efficacy of these agents for preventing recurrent VTE.[245] A randomized open-label trial of fondaparinux versus UFH administered to hemodynamically stable patients with PE for at least 5 days indicated that both agents were equally effective in preventing recurrent VTE.[246] 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 was attained. Furthermore, the incidence of adverse events associated with both therapies was similar. However, only approximately 16% of patients enrolled in this study had either a history of cancer or active cancer.[246] In a recent meta-analysis of trials comparing outcomes with anticoagulants (UFH, LMWH, and fondaparinux) as initial treatment of VTE in cancer patients, LMWH was associated with a significant reduction in mortality rate at 3-month follow-up compared with UFH (relative risk, 0.71; 95% CI, 0.52–0.98).[247] However, no significant difference was found in VTE recurrence between LMWH and UFH. Moreover, no statistically significant differences were found between heparin and fondaparinux in terms of mortality, VTE recurrence, or bleeding events.[247] Current evidence does not support identifying one of these agents as the most efficacious and/or safest choice for patients with cancer, although fully reversible UFH may be preferable in unstable, hospitalized patients with a higher risk of bleeding[194] (see page 730).

Chronic VTE Treatment

Several studies comparing the efficacy and safety of LMWH and oral vitamin K antagonists (e.g., warfarin) in the chronic treatment of VTE in patients with cancer have been performed. In one randomized open-label trial (CANTHANOX), the use of chronic (3 months) enoxaparin (1.5 mg/kg every 24 hours) versus chronic warfarin (INR 2–3) was evaluated after immediate treatment with either LMWH or UFH in 146 cancer patients with VTE.[160] The primary end point of this study was a combined outcome event, including major bleeding and recurrent VTE within 3 months. In the groups receiving chronic enoxaparin and warfarin, 10.5% and 21.1% of patients, respectively, experienced either major bleeding or recurrent VTE (P = .09); fatal bleeding occurred in 0% and 8% of patients, respectively (P = .03). In another study, no significant differences in bleeding or recurrent VTE were observed when patients with active cancer and acute VTE were randomized to either 6 months of enoxaparin (either 1.5 mg/kg or 1 mg/kg every 24 hours) or immediate enoxaparin therapy followed by warfarin to complete 6 months of therapy (ONCENOX trial).[248]

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 treatments, overall.[249] However, bleeding complications were significantly higher for the overall group undergoing warfarin therapy (20% vs. 13% with tinzaparin; P = .01). A subset analysis of the 200 cancer patients enrolled in the LITE trial showed a significantly increased rate of VTE in the group undergoing warfarin therapy at 12 months (16% vs. 7%; P = .044), whereas bleeding rates between the groups were not significantly different.[158]

Finally, the CLOT trial compared the efficacy and safety of immediate dalteparin (200 units/kg daily for 5–7 days) followed by chronic (6 months) therapy with an oral coumarin derivative versus chronic dalteparin therapy (200 units/kg daily for 1 month followed by 150 units/kg for months 2–6) in patients with cancer (most of whom had metastatic disease) after diagnosis of acute proximal DVT or PE, or both.[159] The Kaplan-Meier estimate for recurrence of VTE over the 6-month study period showed significantly decreased risks with dalteparin compared with oral anticoagulants (HR, 0.48; P = .002). This study showed 9% and 17% probabilities of recurrent VTE at 6 months in cancer patients receiving dalteparin or oral anticoagulants, respectively. No significant difference in bleeding rates was seen between the groups.[159] The results of this study support the 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 apparent efficacy difference was observed for development of recurrent DVT only (but not for PE, although the study was not designed to assess differences in outcomes according to type of VTE); and uncertainty regarding whether these results can be extrapolated to LMWHs other than dalteparin. Combining the results of all of 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 LMWHs compared with oral vitamin K antagonists.[250] However, the incidence of VTE was significantly lower for patients receiving LMWH (HR, 0.47; 95% CI, 0.32–0.71).

Increased survival rates have been reported for subgroups of cancer patients undergoing chronic treatment with LMWH versus other VTE therapies or placebo.[251,252] For example, although no survival differences were seen among groups of patients with advanced cancer without VTE receiving either dalteparin or placebo in the FAMOUS study, results from a subgroup analysis of patients with better prognoses (more indolent disease and survival beyond 17 months postrandomization) suggested that 2- and 3-year survival rates were higher for patients receiving dalteparin than those receiving placebo.[194] A post hoc analysis of patients from the CLOT study also showed no differences in 1-year survival 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 compared with patients in the same subgroup receiving an oral vitamin K antagonist.[252] Results of other randomized studies have also showed improvement in median progression-free and/or overall survival of cancer patients receiving LMWHs.[253,254]

In addition, a Cochrane review assessing the antineoplastic properties of anticoagulants found that heparins seem to improve survival in cancer patients with limited-stage disease, and that further research is warranted to identify the most effective regimens and most responsive cancer patient populations.[255] Additional evaluations of the putative antitumor effects of LMWHs are needed before their use as antineoplastic agents can be recommended.

Treatment of CVAD-Related DVT

The central tenet guiding the treatment of CVAD-related DVT is based on whether the device is required for continued treatment of the patient. Device removal is recommended in cases of CVAD-related DVT when the device is no longer required or when contraindications to anticoagulation exist. If device removal is planned, some experts have recommended a short period of anticoagulation (e.g., 5–7 days), if feasible, to reduce the chances of clot embolization on device removal. An assessment of the likelihood and consequences of clot embolization based on the size and position of the device-associated thrombus should be conducted before removal. Anticoagulation therapy is recommended while the catheter is in place (in the absence of contraindications) and for at least 3 months or as long as the catheter remains in place, whichever is longer. If the catheter is required but DVT symptoms persist or the clot progresses despite anticoagulation, the panel recommends catheter removal. Patients with CVAD-related DVT and contraindications to anticoagulation therapy should be followed up for changes in these contraindications as clinically indicated; anticoagulation therapy is recommended after contraindications are no longer present.

No randomized, controlled trials have been reported evaluating the effects of particular therapeutic strategies on outcomes of CVAD-associated VTE. A prospective study of 444 cancer patients with CVAD showed a 4.3% incidence of symptomatic catheter-related thrombosis.[67] Of 19 patients with catheter-related thrombosis, 9 were treated with anticoagulation therapy only, 8 underwent anticoagulation therapy and catheter removal, 1 was treated with catheter removal only, and 1 had no treatment. The duration of anticoagulation therapy was not specified, but evaluation of the 15 patients alive at 24 weeks after diagnosis of catheter-related thrombosis showed that only 2 had residual symptoms. A more recent pilot study of cancer patients with catheter-related, symptomatic UEDVT showed that anticoagulation with dalteparin followed by warfarin (INR 2–3) was not associated with episodes of recurrent VTE and/or line removal as a consequence of thrombosis/infusion failure; major bleeding occurred in 3 patients (4%).[256]

Treatment of SVT

Anticoagulation therapy (e.g., intravenous UFH or a LMWH for at least 4 weeks) is recommended for patients with a nonperipheral catheter–related SVT in proximity to the deep venous system (category 2B; see page 718). Because migratory superficial thrombophlebitis is a characteristic presentation of Trousseau's syndrome, a heightened awareness of this cancer-associated hypercoagulable state is warranted, because indefinite therapy with UFH or LMWH is essential for its treatment.

Catheter removal is recommended for a peripheral catheter–related SVT. Anti-inflammatory medications, warm compresses, and elevation of the affected limb should be used as clinically indicated. These strategies are also recommended for the initial treatment of SVT that is not associated with a peripheral catheter. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients with platelet counts less than 20,000 to 50,000/mcL or with severe platelet dysfunction. Anti-inflammatory agents are recommended for the symptomatic treatment of certain types of SVT only, not for DVT prophylaxis. Only a limited number of studies have evaluated the clinical significance of SVT, its associated progression to VTE, and the effect of anticoagulant agents on its course.[257,258] In a large observational study of patients (N = 844) with symptomatic SVT (≥ 5 cm), 66% had SVT of the greater saphenous vein, and in 20% of these patients the median distance between the thrombus and the saphenofemoral junction was 3 cm or less.[88] In this study, 25% of patients had DVT or PE at inclusion, and 10% of the patients without VTE at study inclusion (i.e., isolated SVT only) who were available at 3-month follow-up subsequently developed thromboembolic complications (e.g., PE, DVT, extension of SVT) despite the use of anticoagulation therapy in approximately 90% of these individuals.[88] A possible limitation of this study is that all of these patients were evaluated in a specialist referral setting. In a prospective assessment of 60 consecutive patients with SVT of the greater saphenous vein, the combined incidence of DVT and SVT events over a 6-month follow-up period was lower in patients treated with twice-daily subcutaneous injections of high-dose heparin (12,500 IU for 1 week, followed by 10,000 IU) for 4 weeks compared with patients receiving 4 weeks of low-dose (5000 IU) heparin (3% vs. 20%; $P = .05$).[259] A pilot study evaluating the effects of once-daily administration of an LMWH, an NSAID, or a placebo for 8 to 12 days on the clinical course of SVT showed no significant differences between treatment and placebo groups with respect to progression to DVT.[260] However, all active treatments reduced the combined rate of DVT and SVT compared with placebo, although no significant differences were observed between active treatment groups.[260] This finding possibly indicates that longer treatment durations may be required.

Treatment of SPVT

The management of patients with SPVT encompasses the use of anticoagulation therapy with or without invasive procedures (e.g., CDT, transjugular intrahepatic portosystemic shunting [TIPS], surgical shunting, surgical resection of bowel) and other medical management (e.g., use of β-blockers), depending on the extent and location of the thrombus, presence of acute symptoms of intestinal infarction, and signs of portal cavernoma or portal hypertension (see page 728). In the absence of contraindications, anticoagulation with UFH or LMWH (preferred) should be initiated, followed by oral anticoagulation for at least 6 months in the case of triggered thrombotic events (e.g., postsurgical setting).[98,100,106,107] The benefit of anticoagulation as initial and long-term therapy in patients with SPVT has been reported in several studies.[94,109,261,262] In a long-term follow-up study of patients with SPVT (N = 95; median follow-up of 41 months) primarily treated with anticoagulation (LMWH, 200 IU/kg per day for 7–10 days followed by oral anticoagulation for 6 months), 45% of patients with acute SPVT (n = 21) had complete recanalization with anticoagulants.[94] Patients requiring resection for intestinal infarction, having incomplete recanalization of thrombus, or having inherited thrombophilia were given lifelong oral anticoagulation in this study. Recurrent VTE occurred in 18.5% of patients overall, and was significantly more frequent among those with concurrent myeloproliferative disorders at presentation than among those without these disorders (70% vs. 13%; $P < .0001$); moreover, recurrent VTE was only observed among patients who did not receive anticoagulation.[94] Gastrointestinal bleeding occurred in 15% of patients and was significantly more frequent among patients with bleeding from esophageal varices at presentation compared with those without prior bleeding

(57% vs. 5%; $P < .0001$). None of the patients receiving oral anticoagulation had bleeding events.[94]

In a recent prospective multicenter study in patients with acute portal vein thrombosis (N = 95) treated with anticoagulation (initial therapy with heparin followed by oral anticoagulation targeting INR 2–3 for 6 months or long-term in patients with permanent prothrombotic disorders or obstruction of mesenteric vein), the 1-year recanalization rate in the portal vein was 38%.[109] The 1-year recanalization rates in the mesenteric and splenic veins were 61% and 54%, respectively. Nonfatal gastrointestinal bleeding occurred in 9% of patients.[109] Anticoagulation seems to lower the risk for recurrent thrombosis in patients with SPVT without increasing the risks for severe bleeding,[94,109,261,262] including in patients with underlying prothrombotic states.[261] However, a recent retrospective study in a large cohort of patients with SPVT (N = 832) showed that the rate of recurrent VTE was not significantly improved with oral anticoagulation with warfarin (10-year recurrence-free survival rate of 89% vs. 77% in patients who did not receive anticoagulation; $P = .38$).[93] Based on multivariate analysis, hormone therapy was the only independent predictor of recurrence. Major bleeding events were reported more frequently among patients who received anticoagulation than among those who did not (26% vs. 19%; $P < .05$); moreover, based on multivariate analysis, the presence of gastroesophageal varices and treatment with anticoagulation were independent predictors of bleeding events.[93] In chronic SPVT, the presence of portal hypertension may increase the risk for bleeding from esophageal varices, and splenomegaly may lead to decreased platelet counts, which can further increase the risks for bleeding events in patients treated with anticoagulation.[92] Thus, in the absence of randomized controlled trials, the issue of long-term or lifelong anticoagulation remains somewhat controversial in patients with SPVT. An individual patient's risk factors for SPVT should be considered when weighing the risks and benefits of long-term anticoagulation. The panel currently recommends lifelong anticoagulation in patients with active cancer, underlying thrombophilia, and/or idiopathic thrombosis.

In patients with acute SPVT with clinical deterioration or progression of thrombosis despite anticoagulation, more invasive approaches using CDT, TIPS or surgical shunting may be required.[98,100,107] Acute thrombosis involving the mesenteric veins is associated with a high risk of intestinal infarction, which is life-threatening and requires immediate surgery to resect necrotic sections of the bowel.[94,96,100,106] CDT therapy has been reported to have some success in acute SPVT in small retrospective studies.[263–266] Thrombolytic therapy may be most suitable when administered locally for patients with recent thrombosis[107,265]; however, this approach should be used with caution because of risks for major bleeding complications.[106,107,263,266] The decision to administer thrombolytic therapy should be based on availability and expertise at the local institution, the location of the thrombus, and evaluation of risks for bleeding in individual patients. In addition, the regimen should be selected based on institutional experience, with decisions made in conjunction with specialists in interventional radiology and vascular surgery.

For patients with acute hepatic vein thrombosis with contraindications to anticoagulation, or for patients with chronic hepatin vein thrombosis for whom medical management alone is unsuccessful, TIPS or surgical shunts may be considered (see page 728). TIPS is an interventional radiologic procedure that creates a portocaval shunt between the hepatic and portal veins, and may be appropriate for patients with an occluded IVC or a portacaval pressure gradient less than 10 mm Hg.[107,267] TIPS may also be appropriate for patients with refractory ascites and progressive hepatic dysfunction despite medical management and/or interventions for recanalization.[267,268] This procedure is less invasive than surgical interventions, and has been successful in reducing portal hypertension, resolving ascites, and improving hepatic function in patients with Budd-Chiari syndrome.[267–272] Although shunt dysfunction or stenosis is common during follow-up, TIPS is associated with promising long-term outcomes, with 5-year transplant-free survival rates of 74% to 78% in recent studies.[267,272] Surgical portosystemic shunts may be appropriate in patients without an occluded IVC, with a portacaval pressure gradient greater than 10 mm Hg, and with preservation of hepatic function.[107,273] The impact of surgical shunts versus other interventions on long-term outcomes is unknown[274]; nevertheless, 5-year survival rates range from 75% to 87% in patients with Budd-Chiari syndrome undergoing successful surgical portosystemic shunts,[275–277] and this procedure may improve survival outcomes

in patients with intermediate-risk prognostic factors as defined by Darwish Murad et al.[278] Surgical shunts seem to have been largely replaced with TIPS recently.[268]

Patients with chronic portal or mesenteric vein thrombosis frequently present with cavernous transformation and/or signs of portal hypertension, the latter of which can lead to complications such as variceal bleeding.[108] Gastroesophageal varices may be seen in 35% to 50% of patients with portal vein thrombosis at presentation,[93,106] and remain a significant independent risk factor for major bleeding in patients with SPVT.[93] Thus, an important goal in the management of patients with chronic portal or mesenteric thrombosis is risk reduction for and prevention of bleeding events.[100,106]

Both β-blockers and endoscopic treatments have been evaluated in the primary and secondary prophylaxis of variceal bleeding in patients at high risk for bleeding events. Several prospective randomized studies comparing the use of variceal banding ligation versus propranolol for primary prophylaxis of variceal bleeding in patients with cirrhosis presenting with high-risk gastroesophageal varices showed that the treatment methods were similarly effective in preventing variceal bleeding (which occurred in 12%–25% of patients treated with ligation and 24%–29% receiving propranolol), with a similar overall mortality rate.[279–281] In one of the studies, patients treated with variceal banding ligation (N = 75) had a significantly decreased incidence of esophageal variceal bleeding compared with those receiving propranolol (5% vs. 25%; $P = .027$), but at the expense of a higher incidence of subcardial variceal bleeding (8% vs. 0%; $P = .027$).[279] In another prospective randomized trial comparing the effectiveness of primary prophylaxis using these methods in patients with cirrhosis (N = 60), ligation was reported to be more effective than propranolol in preventing variceal bleeding (which occurred in 7% vs. 30% of patients, respectively; $P = .043$).[282]

A large randomized study comparing variceal banding ligation with or without propranolol for primary prophylaxis of variceal bleeding in patients with high-risk varices (N = 144) showed that the combined modality did not significantly reduce the risks for bleeding (actuarial probability, 7% vs. 11%; $P = .72$) or death (actuarial probability, 8% vs. 15%; $P = .37$) at 20 months compared with ligation alone.[283] The use of variceal banding ligation and propranolol has also been evaluated in the secondary prophylaxis setting in patients with noncirrhotic portal hypertension at risk for recurrent variceal bleeding. In a recent study (N = 101), the incidence of recurrent variceal bleeding was found to be similar among patients treated with ligation and those receiving propranolol (24% vs. 18%; $P = .625$) for prevention of recurrent bleeding.[284] However, a recent meta-analysis of randomized studies showed that endoscopic treatment (i.e., variceal banding ligation or sclerotherapy) combined with β-blockers was significantly more effective than endoscopic treatment alone in preventing overall recurrent bleeding (OR, 2.20; 95% CI, 1.69–2.85; $P < .0001$) and in decreasing overall mortality (OR, 1.43; 95% CI, 1.03–1.98; $P = .03$), suggesting that combined modality treatment may be preferred as secondary prophylaxis for esophageal variceal bleeding.[285] The panel recommends initiation of β-blockers in patients with chronic portal or mesenteric thrombosis presenting with gastroesophageal varices with or without signs of portal hypertension. In patients with prior variceal bleeding, it may be appropriate to consider variceal banding ligation or sclerotherapy in conjunction with β-blockers (see page 728).

Treatment of PE

Once PE is diagnosed, the panel recommends that patients be risk stratified to determine the advisability of outpatient management and intensity of initial follow-up and treatment.[137,138] Anticoagulation therapy is recommended for all patients with acute PE who have no contraindications (see page 731). In patients with a contraindication to anticoagulation, an IVC filter should be strongly considered (if PE is from lower-extremity, pelvic, or abdominal DVT) and the patient should be closely followed-up to monitor for a change in clinical status that would allow anticoagulation to be instituted (see page 722).[240]

In patients with submassive PE and evidence of moderate or severe right ventricular enlargement or dysfunction, thrombolytic therapy is a therapeutic consideration.[124,240,286] In patients without contraindications to anticoagulation, immediate anticoagulation therapy should be started at PE diagnosis. Risk should be evaluated concurrently with PE diagnosis or as soon as relevant data are available. After the cancer status is assessed in the high-risk patient with PE, the physician should consider thrombolytic ther-

apy and/or pulmonary embolectomy after weighing the severity of the patient's illness and the risk for bleeding. Although IVC filters are typically reserved for patients with a contraindication to anticoagulation, these devices are occasionally placed in patients with severely compromised cardiopulmonary status. If a filter is placed for this indication, a retrievable filter with a wide window of retrievability should be placed to maximize the chances for subsequent filter retrieval once the patient's cardiopulmonary status stabilizes. These patients should be followed up closely and their filters retrieved once they are stable on therapeutic anticoagulation.

A meta-analysis of 9 randomized, controlled clinical studies of unselected patients with acute PE showed that thrombolytic therapy was not superior to anticoagulation therapy with intravenous heparin for reducing mortality or PE recurrence, and was associated with a significantly increased risk for major bleeding.[287] Another meta-analysis of the same 9 clinical trials indicated that patients undergoing thrombolytic therapy were less likely to experience a composite end point of PE recurrence or death than those receiving heparin.[288] However, the difference in PE recurrence rates alone was not statistically significant, and overall bleeding risk was found to be significantly elevated among patients undergoing thrombolytic therapy.[288] In an updated meta-analysis involving 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.[289] However, a significant decrease in recurrent PE or death was observed with thrombolytic therapy in an evaluation of the subset of trials that included patients with major (hemodynamically unstable) PE.[289]

In the randomized, placebo-controlled MAPPET-3 trial of hemodynamically stable patients with submassive acute PE and pulmonary hypertension or evidence of right ventricular dysfunction who received heparin in conjunction with thrombolysis with alteplase or heparin plus placebo, the addition of thrombolysis was associated with significantly decreased incidence of in-hospital mortality and clinical deterioration requiring treatment escalation (primary end point; 11% vs. 25%; $P = .006$). This difference was from a higher incidence of clinical instability in the placebo group, because in-hospital mortality rates were similar between the groups.[290] The clinical end points and other aspects of the trial design have been criticized.[291,292] Reports from several studies evaluating the use of pulmonary embolectomy in patients with acute PE provide support for the use of this procedure in patients with hemodynamically stable or unstable acute PE characterized by right ventricular dysfunction.[293–295] 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 cancer patients. However, no significant difference in bleeding risk was observed in a recent retrospective consecutive case series comparing the safety of percutaneous CDT for upper- or lower-extremity acute symptomatic DVT in patients with or without cancer.[244]

Although the ACCP recommends against the use of thrombolytic therapy or pulmonary embolectomy in most patients with PE, they recommend routine assessment of those with acute PE for thrombolytic therapy.[173] Thrombolytic therapy is recommended in selected patients, such as those with massive PE who are hemodynamically unstable and without a high risk of bleeding.[173,240] Catheter or surgical embolectomy may be recommended in patients with massive PE who have contraindications to thrombolytic therapy or who remain unstable after thrombolysis.[240]

VTE Therapies: Response Assessment

Intensive monitoring of the antithrombotic effects of some anticoagulants is particularly important in patients with cancer.[182] The recommendations for monitoring anticoagulant response included in these NCCN Guidelines may be superseded by written SOPs specific to an institution.

UFH

Heparins indirectly affect the coagulation system through potentiating antithrombin activity, thereby facilitating inhibition of thrombin, factor Xa, and, to a lesser extent, several other activated coagulation factors.[181,296] The aPTT measures the overall activity of the intrinsic and common coagulation pathways and is particularly sensitive to agents that inhibit thrombin.[181,297] Therefore, UFH is most commonly monitored through aPTT during treatment of VTE, and requires the establishment of a therapeutic aPTT range.[181,198,298] Each institution should establish this range using regular calibration of the aPTT therapeutic range against UFH levels of 0.3

to 0.7 units/mL (as determined by factor Xa inhibition using a chromogenic assay) or 0.2 to 0.4 units/mL (as determined by protamine sulfate titration) as recommended by the College of American Pathologists (CAP) and ACCP.[181,298,299] This testing should be performed in the clinical laboratories at each institution according to an institutional SOP, and the aPTT therapeutic range should be printed on the laboratory report. In the event that this information is unavailable, a fixed aPTT therapeutic range of 2 to 2.5 times the control value (i.e., the baseline aPTT for the patient) is recommended by the panel to monitor UFH dosing (see page 731). Monitoring is generally not performed in patients receiving prophylactic doses of subcutaneous UFH.[296]

LMWHs and Fondaparinux

LMWHs act through potentiating the inhibitory activity of antithrombin against factor Xa and to a lesser extent, thrombin.[181] Fondaparinux is a synthetic indirect factor Xa inhibitor that also functions through potentiation of antithrombin activity.[150] Measurement of factor Xa inhibition, not the aPTT, is necessary to monitor the anticoagulant effect of LMWH or fondaparinux, because thrombin inhibition associated with LMWH or fondaparinux is weak or absent, respectively.[150,181] However, only limited data are available on the use of factor Xa inhibition to monitor and adjust LMWH or fondaparinux therapy, and patients receiving these are generally not monitored because of the more predictable dose–response associated with these agents.[181,194] 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 usefulness 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.

DTIs

Lepirudin, argatroban, and bivalirudin are DTIs that do not require antithrombin for anticoagulant activity. Therefore, the anticoagulant effect of these agents can be measured using the aPTT, although results can be affected by the specific DTI and the aPTT assay reagents used.[296] Target aPTT ranges of 1.5 to 2 times control, 1.5 to 3 times control, and 1.5 to 2.5 times control are recommended when using lepirudin, argatroban, and bivalirudin, respectively (see page 726). The aPTT range of 1.5 to 2 times the control for lepirudin is lower than specified by the manufacturer. Similar to heparin, the aPTT-based therapeutic range for lepirudin should be calibrated against lepirudin plasma concentrations. Approximately 50% of patients treated with lepirudin for more than 5 days develop antibodies that prolong the drug's half-life.[300–302] Although rare, reexposure to lepirudin in patients with antibodies has been associated with anaphylactic reactions, particularly when this occurs within 3 months of treatment.[303] These antibodies may cross-react with bivalirudin[304] but not argatroban,[305] and therefore argatroban should be considered in patients recently exposed to lepirudin. Lepirudin is cleared renally, whereas argatroban is metabolized in the liver,[306,307] and therefore significant dose reductions of these agents are necessary in patients with impaired renal and liver function, respectively. Lepirudin and argatroban should be avoided in patients with severely impaired renal and hepatic function, respectively. Bivalirudin, which is predominantly cleared by plasma hydrolysis (80%),[308,309] is preferred in patients with impaired renal and hepatic function.

Warfarin

Warfarin inhibits production of functional forms of vitamin K–dependent anticoagulation factors, such as factors II, VII, IX, and X, and the endogenous anticoagulant proteins, proteins C and S, by the liver.[202] 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 individual patients.[296] The panel recommends a target INR of 2.5 (range, 2–3) for VTE treatment; this range is consistent with ACCP recommendations.[173] Initially, the INR should be checked at least twice weekly during the transition phase from concurrent therapy with a parenteral anticoagulant (i.e., UFH, LMWH, or fondaparinux) to warfarin monotherapy. Once stable INRs are achieved, the frequency of

monitoring can be gradually decreased in a step-wise fashion from once weekly to once monthly. Dose changes; addition of new medications, particularly those with the potential to interact with warfarin; or changes in clinical status should prompt more frequent monitoring.[310] A recent, multicenter, randomized clinical trial showed that computer-assisted dosing of warfarin was superior to dosing directed by experienced providers,[311] and therefore this dosing method should be considered in the management of patients on chronic warfarin therapy. Care should be used when transitioning from a DTI to warfarin in the management of HIT, because all DTIs prolong the INR to a varying degree (the strength of this effect is: argatroban > bivalirudin > lepirudin),[196,296,309,312] and the duration of this effect is extended in argatroban-treated patients with hepatic dysfunction[307] (see page 726).

Reversal of Anticoagulant Activity

The anticoagulant effects of UFH are fully reversible with protamine sulfate, and LMWHs are partially reversed by protamine sulfate (~60%).[313] This agent must be used with caution because it can cause severe hypotension or anaphylactoid reactions, particularly if infused more rapidly than 5 mg/min.[148,149,151,152,181,313–315] Patients with fish allergies, those with previous exposure to protamine (e.g., neutral protamine Hagedorn insulin), and vasectomized or infertile men are at increased risk for allergic reactions[314] (see pages 732–734).

The management of patients with a supratherapeutic INR is a common clinical challenge. In many cases, the effects of warfarin therapy in patients with elevated INRs who are not bleeding can be reversed through withholding the warfarin dose and, depending on the INR, administering oral vitamin K_1.[202,310,316] However, those with serious or life-threatening bleeding or those needing rapid preparation for urgent/emergent invasive procedures associated with bleeding risk require intravenous vitamin K_1 and prothrombin complex concentrate (PCC) with or without fresh frozen plasma (FFP), FFP alone if no PCC is available, or recombinant human factor VIIa (rhFVIIa) to reverse the effects of warfarin.[310] Administration of intravenous vitamin K_1 alone is insufficient in a critical situation such as this because it requires 4 to 6 hours for it to begin taking effect on warfarin reversal.[317] Because warfarin acts through inhibiting production of functional vitamin K–dependent clotting factors (factors II, VII, IX, and X) and proteins S and C, administering a 3-factor PCC containing therapeutic quantities of factors II, IX, and X can facilitate the reversal of its anticoagulation effect. However, evidence shows that 3-factor PCC should be supplemented with FFP to optimize warfarin reversal.[313,318] FFP alone can be given in place of PCC plus FFP if PCC is not available, but a disadvantage of this approach is the time delay associated with the preparation, delivery, and infusion of FFP.[313,319] rhFVIIa, a synthetic analogue of native factor VIIa, can also be used to rapidly reverse warfarin in place of either FFP or PCC.[310,320,321] A small risk of anaphylaxis (~ 3 per 10,000) is associated with the intravenous administration of vitamin K_1, especially when it is administered more rapidly than 1 mg/min,[313,322] and PCC and rhFVIIa have been associated with a low risk of thromboembolic events.[323,324]

Specific agents to reverse many of the newer anticoagulants do not exist. Hence, limited evidence is available to guide the management of patients treated with these drugs who are in need of anticoagulant reversal. For example, no agents are available to reverse the anticoagulant activity of inhibitors of factor Xa (e.g., fondaparinux and the anti–factor Xa activity of LMWH) or thrombin (e.g., DTIs). Nevertheless, intravenous rhFVIIa, which rapidly induces thrombin generation, can be administered to help reduce the anticoagulant effects of LMWHs, DTIs, and fondaparinux.[313,321,325,326] Other possible strategies include use of FFP or cryoprecipitate; desmopressin acetate (DDAVP), which stimulates release of factor VIII and von Willebrand factor; antifibrinolytic agents which block plasmin activity (i.e., the enzyme which breaks down fibrin clots); or mechanical strategies such as hemofiltration and hemodiafiltration, which can remove small-molecule anticoagulants.[313,327] However, DDAVP is effective only for 3 or 4 doses, after which tachyphylaxis develops[328,329] (see pages 732–734). Although rare, DDAVP has also been associated with hyponatremia.[328]

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 (see page 736).[330]

Although anticoagulation therapy failure has many potential causes, an initial determination of whether the INR or aPTT is within the therapeutic range is important for patients with recurrent VTE who are receiving warfarin or UFH, respectively. When INR or aPTT values are subtherapeutic, one obvious option is to increase the anticoagulant dose to a therapeutic level.

Although anticoagulation therapy can fail in patients receiving warfarin, UFH, LMWH, or fondaparinux if the prescribed anticoagulant dose is inadequate, other factors to consider include patient adherence to self-administered medications, such as oral vitamin K antagonists or subcutaneously administered anticoagulants, and the dosing frequency for patients receiving LMWH.[330] For example, an increased risk of VTE recurrence was reported in one study of patients with cancer receiving once-daily enoxaparin in the acute therapy setting.[331] 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 (e.g., LMWH, fondaparinux).[332]

INR or aPTT values may be subtherapeutic when inadequate anticoagulant dosing is not the direct cause of recurrent VTE. For example, warfarin resistance (i.e., inability to reach a therapeutic INR on warfarin doses typically used to treat VTE) can be caused by genetic variability associated with the enzymatic metabolism of warfarin, or the concomitant administration of medications that interact with warfarin.[333,334] An option for patients undergoing warfarin therapy and exhibiting a subtherapeutic INR is a switch to a 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 that reported a low VTE recurrence rate for patients treated with LMWH after failure of warfarin therapy.[335] Likewise, heparin resistance (i.e., inability to reach therapeutic aPTT on heparin doses typically used to treat VTE), though rare, can occur as a result of pharmacokinetic or biophysical/physiologic limitations of heparin therapy.[336]

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.[330,336] Diagnostic testing to identify the presence of syndromes described earlier is critical to the management of VTE in these patients.[330] In particular, clinical suspicion of HIT should be high when recurrent VTE is observed in a cancer patient receiving heparin-based therapy or who received this 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 heparin-based therapy is an option after fondaparinux fails to prevent VTE recurrence and vice versa.

Placement of an IVC filter is an option for treating patients with PE or progression of central DVT despite therapeutic anticoagulation with UFH, LMWH, or fondaparinux, although filters should be avoided in the setting of HIT or migratory thrombophlebitis because of the systemic nature of these coagulopathies.[90,91]

Diagnosis and Management of HIT

Specific guideline recommendations regarding HIT are available from the ACCP.[196] 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.[337] In another study, 2.7% of patients treated with UFH developed HIT.[338] HIT is triggered when administration of heparin displaces platelet factor 4 (PF4; released by activated platelets) into the circulation, which then binds heparin and forms an immunogenic PF4/heparin complex leading to the development of antibodies. These antibodies increase platelet clearance and can activate platelets, resulting in release of procoagulant microparticles and increased thrombin generation.[196,339] The end result is a consumptive thrombocytopenia and profound prothrombotic state that triggers symptomatic thromboembolism in as many as 75% of patients.[196,339] Clinical evidence of HIT includes devel-

opment of thrombocytopenia, formation of necrotic lesions at injection sites, arterial thromboembolic complications, and/or development of VTE.[340,341] HIT typically occurs 5 to 10 days after initial exposure to heparin-based products or in rapid-onset HIT, or within 1 day after administration of heparin in patients previously exposed to these agents within 100 days.[196] Less common is delayed-onset HIT, which can occur days or weeks after heparin therapy has been discontinued.[339]

Some evidence indicates that cancer patients are at increased risk of developing HIT and HIT-related VTE,[342,343] although this has not been firmly established. HIT has been associated with the use of both LMWHs and UFH. Increased rates of HIT were observed in patients receiving heparin-based therapy who were previously exposed to this therapy.[344] Results of some studies indicate that the frequency of HIT with LMWH and UFH is similar,[344,345] whereas other studies suggest a lower incidence of HIT in patients receiving LMWH relative to those receiving UFH.[338,346–348] Greinacher et al.[349] have suggested that factors such as anticoagulant dose (i.e., 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, because a lower relative incidence of HIT with LMWH was primarily observed for surgical patients receiving prophylactic doses of anticoagulant therapy.

A diagnosis of HIT is based on both clinical and serologic evidence.[196] Hence, the presence of clinical sequelae of HIT (e.g., thrombocytopenia [a drop in platelet count > 50%], thrombosis) and anti-PF4/heparin antibodies (i.e., HIT antibodies) are needed for a diagnosis. Furthermore, because most HIT antibodies do not activate platelets, a negative test result is more useful for excluding the diagnosis than a positive test result is for confirming it. In other words, as mentioned by Greinacher,[350] "all HIT is caused by platelet activating antibodies, but not all PF4/heparin antibodies cause HIT." The specificity of platelet activation assays (i.e., functional assays), such as the serotonin release assay (SRA), is higher than antigen assays, such as the PF4/heparin enzyme-linked immunosorbent assay, which detect the presence of HIT antibodies but do not assess their ability to activate platelets.[196]

The diagnosis of HIT is complicated by the high frequency of heparin use in hospitals; the presence of HIT antibodies, which do not activate platelets; possible delays in obtaining serologic test results; and multiple causes of thrombocytopenia in patients receiving heparin-based products. In addition, increased bleeding risks are associated with substitution of a DTI for heparin. Therefore, a high level of clinical suspicion must be present before a patient is treated for HIT.[350]

The 4T's score is a simple, validated tool designed to assess the probability of HIT based on specific characteristics of 4 clinical parameters: thrombocytopenia; timing of the onset of platelet fall; presence of thrombosis or other clinical sequelae; and evidence of other potential causes of thrombocytopenia (see page 725).[351–353] Each of these 4 parameters is weighted (i.e., using a score of 0–2) according to how likely it reflects a HIT diagnosis; a total score of 0 to 8 is possible. Total scores are grouped into 3 categories, which classify the patient as being at low- (0–3), medium- (4–5), or high-risk (6–8) of HIT.[353] As described for HIT antibody testing, evidence suggests that the negative predictive value of this assessment tool is considerably higher than its positive predictive value; hence, this tool is more likely to be useful in identifying patients at low risk of HIT.[352,354]

In patients receiving anticoagulation therapy with UFH or LMWH, 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. If HIT is suspected, patients should be evaluated using the 4T's score. Recommendations for patients classified as being at low risk for HIT include the following: consider alternative causes of thrombocytopenia; weigh the risks/benefits of continued therapy with heparin versus a DTI or fondaparinux; consider maintaining anticoagulation with heparin; monitor their clinical status; and consider HIT antibody testing in select patients based on clinical judgement. Patients classified as being at moderate/high risk of HIT based on the 4T's score should initially be managed as having HIT. HIT antibody testing should be ordered, although immediate discontinuation of heparin-based products and administration of an alternative anticoagulant, typically a DTI, is recommended. For patients receiving warfarin, it should be discontinued and reversed with vitamin K. In

addition, a 4-extremity duplex ultrasound is recommended to identify subclinical DVT.

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

The results of HIT antibody testing further direct management. For example, options for patients with a negative HIT antibody test result include a reassessment of anticoagulation therapy based on the 4T's score, and consideration of SRA testing or repeat HIT antibody testing in the context of the pretest probability of HIT. Repeat testing or a negative SRA test result can rule out a HIT diagnosis in patients with a negative HIT antibody test. The management of patients with a positive HIT antibody test on initial testing should be reevaluated based on the 4T's score pretest probability. Patients with a moderate/high 4T's score should be managed according to recommendations for patients with a diagnosis of HIT, whereas SRA testing should be considered in those with a low pretest probability, with test results directing further management.

Anticoagulants for the Treatment of HIT: *DTIs:* DTIs available in the United States for the management of HIT include argatroban, lepirudin, and bivalirudin.[196] The effectiveness of lepirudin in treating HIT was shown in several prospective clinical trials.[355–358] A pooled analysis from the 3 prospective trials evaluating lepirudin in patients with confirmed HIT (N = 403) showed that lepirudin significantly reduced the combined end point of death, limb amputation, and occurrence of new thrombotic complications compared with historical controls (29.7% vs. 52.1%; P = .0473).[358] This difference was largely attributable to a decreased incidence of new thrombotic events with lepirudin (11.9% vs. 32.1%; P = .0008). However, the incidence of major bleeding was significantly higher with lepirudin compared with historical controls (29.4% vs. 9.1%; P = .0148).[358] The benefit of lepirudin compared with historical controls was also shown in the subset of patients with HIT and concurrent thrombosis, although bleeding events requiring transfusion support occurred significantly more frequently with lepirudin.[357]

Two prospective clinical trials evaluated the activity of argatroban in patients with clinically diagnosed HIT, with or without concurrent thrombosis.[359,360] In the initial trial, argatroban significantly reduced the combined end point of death, limb amputation, and occurrence of new thrombotic events among patients with HIT without thrombosis (n = 160) compared with historical controls (25.6% vs. 38.8%; P = .014); no significant differences in the combined end point were noted among patients with HIT and thrombosis (n = 144).[359] Similarly, results from the second trial of argatroban showed significantly decreased incidence of the combined end point with argatroban compared with historical controls in patients with HIT without thrombosis (n = 189; 28.0% vs. 38.8%; P = .04), but not in patients with HIT and thrombosis (n = 229; 41.5% vs. 56.5%; P = .07).[360] In both trials, argatroban was shown to significantly decrease the incidence of death from thrombosis and the incidence of new thrombosis compared with controls (P < .05) in both groups of patients with HIT with or without concurrent thrombosis.[359,360]

Both argatroban and lepirudin are approved by the FDA for the immediate treatment of HIT.[306,307] Argatroban is primarily metabolized by the liver, and prolonged clearance of this agent has been seen in patients with hepatic insufficiency.[307] Lepirudin is primarily excreted by the kidneys and may accumulate in patients with renal dysfunction, depending on the extent of renal impairment.[306] 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. A lepirudin dosing regimen that is less aggressive than the standard regimen has been recommended, and the results of other studies support this recommendation.[196,306,361–365] In patients with normal renal function, lepirudin administered at a dose of 0.08 mg/kg/h (and omitting the initial bolus dose) is recommended; a further dose reduction to 0.04 mg/kg/h is recommended for patients with moderate renal impairment (C_{cr}, 30–60 mL/min).[365] Similarly, the manufacturer recommended dose for argatroban may be too high, especially for the treatment of HIT in critically ill patients.[362,366,367] Argatroban administered at a reduced dose of 1 mcg/kg/min may be adequate to provide sufficient anticoagu-

lation.[367] Dose reductions have also been suggested for bivalirudin,[368] another DTI, when used off-label in the treatment of HIT[369] and in patients with HIT and hepatic and/or renal insufficiency or those who are critically ill.[309,370,371] Although some of the pharmacologic characteristics of bivalirudin are advantageous in the setting of HIT (e.g., short half-life, enzymatic metabolism), data regarding its use in HIT are limited.[309]

The panel recommends a DTI as the preferred treatment for the immediate management of HIT. No head-to-head trials comparing different DTIs in the treatment of HIT have been published. Clinician experience and comfort level with the agents used for the immediate treatment of HIT should be considered when deciding therapy. Use of argatroban and lepirudin should be avoided in patients with hepatic failure and severe renal insufficiency, respectively.

Fondaparinux: These NCCN Guidelines also include the off-label use of fondaparinux as an alternative to parenteral DTIs in the treatment of a current episode of HIT without thrombosis.[372] Advantages to using fondaparinux in this setting, in addition to subcutaneous administration, include its lack of INR prolongation when administered concomitantly with warfarin. Although the long half-life of fondaparinux is a disadvantage when anticoagulation reversal is necessary, a possible benefit may include a decreased risk of rebound hypercoagulability.[373] Furthermore, unlike DTIs, aPTT testing is not used to monitor response to fondaparinux, thereby eliminating problems associated with warfarin prolongation of the aPTT when overlapped with a DTI. Fondaparinux has been used in small numbers of patients with HIT and generally seems to be safe.[374–376] There have been rare reports of an association between fondaparinux use and development of HIT, although in most cases patients had prior exposure to UFH or LMWH.[377–380] Investigators have also suggested that use of fondaparinux in 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.[196,373] Fondaparinux is included in the guidelines as a category 2B option for the immediate management of HIT (see page 726).

Warfarin: The panel recommends against giving warfarin therapy to patients with a moderate or high pretest probability of HIT by the 4T's score. For patients receiving warfarin, it should be discontinued and reversed with vitamin K.[196] Warfarin should not be initiated in patients with HIT until after platelet count recovery because of the potential for skin necrosis and/or venous gangrene, which can result from warfarin-induced reductions in protein C levels in the setting of profound activated coagulation from HIT.[196,381] After platelet recovery (e.g., ≥ 150,000/mcL or when platelets return to baseline), warfarin should be overlapped with a DTI or fondaparinux for at least 5 days; the DTI or fondaparinux should be discontinued only after the INR has reached the intended target range (INR 2–3) for 24 hours. Because both DTIs and warfarin reduce thrombin activity, coadministration of a DTI and warfarin produces a combined effect on the laboratory measurements of both aPTT and INR. However, concurrent therapy, compared with warfarin monotherapy, exerts no additional effect on vitamin K–dependent factor X activity. Therefore, the anticoagulation impact of warfarin may be underestimated in the presence of a DTI. Because argatroban has the lowest affinity for thrombin of the 3 DTIs, higher molar plasma concentrations of argatroban are needed to prolong the aPTT; hence, prolongation of INR is more pronounced with argatroban compared with the other DTIs.[312,382] A higher target INR should therefore be achieved before argatroban is discontinued.[196,307,382] Once argatroban is discontinued, a repeat INR and aPTT should be obtained 4 to 6 hours later to determine whether the INR is therapeutic on warfarin monotherapy. Alternatively, chromogenic factor X levels (which are not affected by DTIs) can be used to monitor warfarin activity during transition from cotherapy with argatroban.[383] The duration of warfarin therapy is dependent on whether HIT is accompanied by thrombosis. In patients with HIT and thrombosis, the duration of therapy is dictated by the nature of the thrombotic event (3 months for DVT, 6 months for PE). In patients with HIT without thrombosis, at least 1 month of warfarin therapy is recommended[339] (see page 726).

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.[384] The risks and probability of success of the interventions should also be considered. 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 when 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 panel recommends VTE thromboprophylaxis for all hospitalized patients with cancer who do not have contraindications to this therapy, and also emphasizes that an increased level of clinical suspicion of VTE should be maintained for cancer patients. After hospital discharge, the panel recommends that cancer patients in a high-risk setting for VTE (e.g., patients who have undergone cancer surgery, those with multiple myeloma) continue to receive VTE prophylaxis, with the duration of anticoagulation determined by the clinical situation. Careful evaluation of cancer patients in whom VTE is suspected, and prompt treatment and follow-up for those 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:

- Benefits and risks of VTE prophylaxis in patients with long durations of severe thrombocytopenia (e.g., those with acute leukemia, bone marrow transplant recipient)
- VTE prophylaxis in cancer patients with a history of CVAD-related DVT at risk for developing a new CVAD-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 LMWHs in cancer patients with renal insufficiency
- IVC filters: indications for placement of retrievable versus permanent filters; triggers for filter removal; and relative efficacy and morbidity of the 2 filter types
- Thrombolytic therapy in cancer patients with PE, including those with submassive PE characterized by right ventricular dysfunction/enlargement, or "massive DVT": effects on morbidity and mortality
- Benefits and risks of extended VTE prophylaxis in ambulatory medical oncology patients (e.g., patients with multiple myeloma)
- Simple VTE risk assessment tools for stratifying cancer patients
- Long-term surveillance of cancer patients at risk for VTE
- Effects of introduction of NCCN Guidelines for VTE on management of cancer patients
- Treatment of incidental thrombosis (e.g., PE, pelvic vein, mesenteric or portal vein) in cancer patients: whether all patients or only a subset should be treated
- Treatment guidelines for cerebral venous sinus thrombosis
- Treatment guidelines for VTE in pregnant patients with cancer
- Treatment guidelines for VTE in patients with primary and metastatic brain tumors
- Bridging anticoagulation guidelines for cancer patients requiring invasive procedures

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Individual Disclosures of the NCCN Venous Thromboembolic Disease Panel					
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