NCCN Clinical Practice Guidelines in Oncology™

Venous Thromboembolic Disease

V.2.2006

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

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

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

See NCCN Categories of Consensus

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Summary of the Guidelines updates

Summary of major changes in the 2.2006 version of the Venous Thromboembolic Disease guidelines from the 1.2006 version include:

- Under “Immediate”: Revised dosing of Dalteparin and Fondaparinux (VTE-D).
- Added new bullet “Failure of anticoagulation” (VTE-F).
VENOUS THROMBOEMBOLISM PROPHYLAXIS

AT RISK POPULATION

- Adult patient
- Diagnosis of cancer or clinical suspicion of cancer\(^a\)
- Inpatient

INITIAL PROPHYLAXIS

<table>
<thead>
<tr>
<th>Relative contraindication to anticoagulation treatment(^b)</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic anticoagulation therapy(^c) (category 1) ± Sequential compression device (SCD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical prophylaxis (options)(^d)</td>
<td></td>
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<tr>
<td>‣ SCD</td>
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<tr>
<td>‣ Graduated compression stockings</td>
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</tbody>
</table>

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

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

DIAGNOSIS

Clinical suspicion of DVT:
- Swelling of unilateral extremity
- Heaviness in extremity
- Pain in extremity
- Swelling in supraclavicular space
- Catheter dysfunction; If catheter is present See Catheter-Related DVT (DVT-3)

WORKUP/IMAGING

- Comprehensive medical history and physical examination
- Imaging:
  - Venous ultrasound

IMAGING FINDINGS

- Positive for DVT
- Negative or Indeterminate
  - Continued clinical suspicion of DVT
    - Venous imaging:
      - CT scan
      - Magnetic resonance venogram (MRV)
      - Venogram
  - Negative

ADDITIONAL IMAGING

- Anti-inflammatory medications
- Symptomatic treatment, including warm compresses and elevation
- Re-evaluate if there are progressive symptoms, consider anticoagulationb

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a Imaging recommendations reflect initial diagnostic workup of an individual who has not previously been diagnosed with DVT.
b See Therapeutic Anticoagulation Treatment for DVT, PE, Catheter-Associated Thrombosis (VTE-D).
DVT: TREATMENT

**DVT TYPE**

**Upper extremity**
- Relative contraindications to anticoagulation
  - Yes → Follow until relative contraindication is resolved or progression of DVT
  - No → Anticoagulation therapy
    - Consider catheter-directed thrombolytic therapy for massive DVT

**Calf**
- Relative contraindications to anticoagulation
  - Yes → Progression → Follow-up for DVT progression initially at one week
  - No → Continue to follow as clinically indicated

**Relative contraindications**
- Yes → IVC filter
- No → Re-evaluate as clinically indicated

- Superior vena cava (SVC)
- Pelvic/iliac/IVC
- Femoral/popliteal
- Mechanical caval filtering device
- Relative contraindication persists
  - Yes → Re-evaluate as clinically indicated
  - No → Anticoagulation therapy
- Anticoagulation therapy
  - Consider catheter-directed thrombolytic therapy for massive DVT

**Catheter-related thrombosis**
- See Catheter-Related Thrombosis Treatment (DVT-3)

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See Therapeutic Anticoagulation Treatment for DVT, PE, Catheter-Associated Thrombosis (VTE-D).
See Relative Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
See Elements for Consideration in Decision Not To Treat (VTE-E).
CATHETER-RELATED DVT: DIAGNOSIS

**POPULATION**
- Clinical suspicion of catheter-related DVT
  - Unilateral arm/leg swelling
  - Pain in supraclavicular space or neck
  - Dysfunctional catheter

**IMAGING**
- Ultrasound
- CT/MRI
- Venogram

**TREATMENT**
- **Catheter required**
  - Relative contraindications to anticoagulation
    - Yes
      - Follow for change in relative contraindications as clinically indicated
    - No
      - Remove catheter

- **Catheter not required**
  - Remove catheter
  - Relative contraindications to anticoagulation
    - Yes
      - Re-evaluate for risk/benefit of anticoagulation
    - No
      - Anticoagulate per DVT protocol for 1-3 mo (See DVT-2)

- **No DVT**
  - Evaluate for other causes
  - Anticoagulate per DVT protocol for as long as catheter is in place and for 1-3 mo after catheter removal (See DVT-2)

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See Relative Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
See Elements for Consideration in Decision Not To Treat (VTE-E).
Consider anticoagulation before catheter removal.

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**PE: DIAGNOSIS**

**POPULATION**
- Clinical suspicion of PE:
  - Current DVT or recent history of DVT
  - Unexplained shortness of breath, chest pain, tachycardia, apprehension, tachypnea
  - Syncope
  - $O_2$ desaturation

**WORKUP**
- Comprehensive medical history and physical examination
- Chest x-ray
- EKG

**IMAGING**
- CT Angiography (CTA)
- Pulmonary angiography (rarely used unless coupled with clot extraction or thrombolytic therapy)
- VQ scan (Lung scan) (if patient has renal insufficiency or uncorrectable allergy to contrast)

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**PE: TREATMENT**

- **Relative contraindications to anticoagulation**
  - Yes → Mechanical IVC device
  - No → Anticoagulation therapy

- **Relative contraindications persist**
  - Yes → Continue anticoagulation therapy
  - No → Follow frequently for change in relative contraindications

- **Upon admission:**
  - Normal: Continue anticoagulation therapy
  - Abnormal: Consider cancer status, thrombolytic therapy for massive PE or submassive PE with moderate or severe right ventricular dysfunction, consider embolectomy, consider IVC filter

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- **Anticoagulate per DVT protocol (See DVT-2)**

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**a** See Relative Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
**b** See Clinical Scenarios Warranting Consideration of Filter Placement Indications (VTE-F).
**c** See Therapeutic Anticoagulation Treatment for DVT, PE, Catheter-Associated Thrombosis (VTE-D).
**d** See Elements for Consideration in Decision Not To Treat (VTE-E).
# Risk Factor Assessment

1. **Age**
2. **Prior VTE**
3. **Familial thrombophilia**
4. **Active cancer**
5. **Trauma**
6. **Major surgical procedures**
7. **Acute or chronic medical illness requiring hospitalization or prolonged bed rest**
8. **Central venous catheter/IV catheter**
9. **Congestive heart failure (CHF)**
10. **Pregnancy**
11. **Regional bulky lymphadenopathy with extrinsic vascular compression**

**Modifiable risk factors:**
- **Lifestyle (diet, environment):** Smoking, tobacco, obesity, activity level/exercise

**Therapeutic agents associated with increased risk:**
- **Chemotherapy**
- **Exogenous estrogen compounds**
  - Hormone Replacement Therapy (HRT)
  - Oral contraceptives
  - Tamoxifen/Raloxifene
  - Diethylstilbestrol
- Thalidomide/lenalidomide

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

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### RELATIVE CONTRAINDICATIONS TO PROPHYLACTIC OR THERAPEUTIC ANTICOAGULATION TREATMENT

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

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INPATIENT PROPHYLACTIC ANTICOAGULATION THERAPY¹, ²

- **LMWH:**³
  - Dalteparin 5,000 units subcutaneous daily
  - Enoxaparin 40 mg subcutaneous daily
  - Tinzaparin 4,500 units (fixed dose) subcutaneous daily or 75 units/kg subcutaneous daily
  - Pentasaccharide³
  - Fondaparinux 2.5 mg subcutaneous daily
  - Unfractionated Heparin: 5,000 units subcutaneous 3 times daily

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

²Follow institutional standard operating procedures (SOP) for dosing schedules, if no SOP then use the American College of Chest Physicians (ACCP) recommendations. Geerts WH, Pineo GF, Heit JA, et al. Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126[suppl 3]:338-400. (www.chestjournal.org)–See sections 1.0, 2.0, 3.5, 3.6, 4.0, 6.0, and 7.0.

³LMWH must be used with caution in patients with renal insufficiency and failure. Dose adjustments may be required.

For Diagnosis and Treatment of Heparin-Induced Thrombocytopenia (HIT), See (VTE-G)
## THERAPEUTIC ANTICOAGULATION TREATMENT FOR DVT, PE, AND CATHETER-ASSOCIATED THROMBOSIS

### Immediate:
- **Low-molecular-weight heparin (LMWH)**
  - Dalteparin (200 units/kg subcutaneous daily)
  - Enoxaparin (1 mg/kg subcutaneous every 12 hours)
  - Tinzaparin (175 units/kg subcutaneous daily)
- **Pentasaccharide**
  - Fondaparinux (5.0 mg [< 50 kg]; 7.5 mg [50-100 kg]; 10 mg [> 100 kg] subcutaneous daily)
- **Unfractionated heparin (IV)** (80 units/kg load, then 18 units/kg per hour, target aPTT to 2.0-2.9 x control)

### Long Term:
- LMWH is preferred as monotherapy without warfarin in patients with proximal DVT or PE and prevention of recurrent VTE in patients with advanced or metastatic cancer
- **Warfarin** (2.5-5 mg every day initially, subsequent dosing based on INR value; target INR 2.0-3.0)

### Duration of Long Term Therapy:
- Minimum time of 3-6 mo for DVT and 6-12 mo for PE
- Consider indefinite anticoagulation if active cancer or persistent risk factors
- For catheter associated thrombosis, anticoagulate as long as catheter is in place and for 1-3 mo after catheter removal

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1. Agent selection based on:
   - Renal failure (Cr < 30mL/min)
   - Inpatient/Outpatient
   - FDA approval
   - Cost
   - Ease of administration
   - Monitoring
   - Ability to reverse anticoagulation

2. Initiate all agents concomitantly with warfarin. For patients who will be switched to long term warfarin, discontinue parenteral therapy when International Normalized Ratio is between 2-3 for 2 consecutive days. Studies support a minimum of 5 days of heparin.


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CLINICAL SCENARIOS WARRANTING CONSIDERATION OF FILTER PLACEMENT

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

1 See Relative Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
DIAGNOSIS AND TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

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

Diagnostic Workup:
- Rule out other causes of thrombocytopenia (ie, chemotherapy, other drugs, DIC, TTP, antiphospholipid syndrome)
- Assess for heparin-associated antibody (ELISA or agglutination assay for platelet factor-4 heparin antibody or serotonin release assay)

Treatment:
- Immediate Management:
  - Discontinue UFH or LMWH and administer a direct thrombin inhibitor (DTI)
    - Argatroban (avoid use in hepatic failure; 2.0 mcg/kg/minute IV infusion, target aPTT 1.5-3.0 x control)
    - Lepirudin (avoid use in renal insufficiency; 0.1 mg/kg/hour IV infusion, target aPTT 1.5-2.0 x control)
    - Bivalirudin (off-label use; 0.15-.20 mg/kg/hour IV infusion, target aPTT 1.5-2.5 x control)
  - Treat with DTI presumptively until antibody results are available and confirmed, especially if clinical suspicion is high or patient requires ongoing anticoagulation
  - Do not transfuse platelets
  - Start warfarin when platelet count recovered to > 100-150,000/mcL; overlap warfarin and DTI or fondaparinux for at least 5 days
  - Discontinue DTI when therapeutic effect of warfarin achieved
  - Argatroban and bivalirudin falsely elevate INR
- Long-term Management:
  - Continue warfarin
  - Target INR of 2.5 (range 2.0-3.0)
  - Complete 1 month of anticoagulation if no thrombosis or other indication to continue (all patients with confirmed HIT require anticoagulation for 1 month because of the high ongoing risk of thrombosis after discontinuing heparin)
  - Complete at least 3-6 months of anticoagulation or longer as indicated by thrombotic event

1Rapid onset HIT (occurs upon exposure to UFH or LMWH for < 2 days) and delayed onset HIT (occurs days to weeks after UFH or LMWH has been stopped) are less common.
2Acceptable alternative agents for special circumstances: bivalirudin (off-label IV DTI), fondaparinux (off-label SC anti-factor Xa inhibitor).

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Venous Thromboembolic Disease

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Venous thromboembolic disease is a common and life threatening condition in cancer patients.1,2 Results from a recent retrospective study of 66,106 hospitalized adult neutropenic cancer patients showed that 2.74% to 12.10% of these patients, depending on the type of malignancy, experienced a venous thromboembolism (VTE) during first hospitalization.1 These NCCN VTE guidelines specifically outline strategies to prevent and treat VTE in adult inpatients with either a diagnosis of cancer or for whom cancer is clinically suspected. These guidelines are characterized by iterative evaluations of the therapeutic advantages of implementing pharmacologic anticoagulation measures based on both the perceived risk of bleeding (i.e., contraindications to anticoagulation) and the cancer status of the patient.

The definition of VTE includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). In these guidelines, DVT is divided into 4 categories, which differ in terms of associated morbidity, treatment, and long-term effects. These categories include upper extremity; lower extremity/distal (e.g., calf); central/proximal (e.g., superior vena caval (SVC), pelvic, iliac, inferior vena caval (IVC), femoral, and popliteal); and catheter-related DVT.

The association of VTE with underlying malignancy was first reported by Armand Trousseau in 1865 and is supported by the results of more recent studies.3-5 Pathophysiologic explanations of the etiology of VTE in cancer include known hypercoagulability (e.g., procoagulants such as tissue factor from cancer cells), vessel wall damage, and vessel stasis from direct compression.6-8 However, the actual prevalence of tumor-induced VTE is unknown, in part because of the frequent presence of confounding risk factors for VTE that occur in patients with cancer, such as prolonged immobilization, surgical procedures, and chemotherapeutic regimens9 (see following section on VTE Risk Assessment in Patients with Cancer).

The occurrence of VTE has been reported to increase the likelihood of death for cancer patients by 2- to 8-fold.10-14 For example, gynecologic oncology patients with PE were found to have a 6-fold increase in risk of death at 2 years compared with similar patients without PE.14 Furthermore, VTE has been reported to be the most common cause of death at 30-day follow-up for cancer patients undergoing surgery.15

The critical need for the development of clinical practice guidelines focusing specifically on VTE in cancer patients was further shown by...
the results of the recent Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey. Responding surgeons and medical oncologists reported use of VTE prophylaxis in only approximately 50% and 5% of their cancer patients, respectively. These results are of particular concern when juxtaposed with a recent review of postmortem reports that showed that approximately 80% of cases of fatal PE occurred in nonsurgical patients.

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

**VTE Risk Assessment in Patients with Cancer**

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

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

A number of specific agents used in cancer treatment are associated with an increased risk of developing VTE. A detailed listing of these agents is not provided here; rather, the guidelines describe some of the evidence for the association of 3 representative classes of cancer drugs (cytotoxic chemotherapeutic regimens, hormone therapy with estrogenic compounds, and anti-angiogenic therapy) with increased VTE risk.
The association of cytotoxic chemotherapy with the development of VTE in cancer patients has been shown in several studies. For example, in one population-based case-control study, odds ratios of 6.53 and 4.05 for development of a VTE were determined when patients with malignant neoplasm who were receiving chemotherapy and patients with malignant neoplasm not receiving chemotherapy, respectively, were compared with patients without malignant neoplasm. In another retrospective study, the annual incidence of VTE was 10.9% in patients with colorectal cancer treated with chemotherapeutic regimens. 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. Diethylstilbestrol phosphate used in combination with doxorubicin for the treatment of hormone-refractory prostate cancer was reported to increase VTE risk when compared with use of doxorubicin alone. Use of estrogenic compounds such as hormone replacement therapy or oral contraceptive agents has also been associated with increased risk of developing VTE. Evidence has been presented to support the association of certain anti-angiogenic therapies (e.g., thalidomide in combination with doxorubicin, and lenalidomide in combination with dexamethasone) with an increased incidence of VTE when used in the treatment of multiple myeloma. Other agents used in supportive cancer care (e.g., hematologic growth factors) have also been associated with the development of VTE. Concomitant use of therapies associated with development of VTE may further increase VTE risk.

A number of other VTE risk factors, although not exclusive to cancer patients, are commonly found in this population. These include recent surgery, hospitalization, and prolonged immobilization. For example, Heit reported odds ratios of 21.72 and 7.98 for the development of VTE in cancer patients hospitalized or confined to a nursing home with and without recent surgery, respectively, compared with non-institutionalized patients who had not recently undergone surgery. In addition, a history of prior VTE was identified as an independent risk factor for developing a future VTE. For example, 12-month cumulative incidences of recurrent VTE of 20.7% and 6.8% were reported for patients with and without cancer, respectively, undergoing anticoagulant treatment. More advanced age, a common characteristic of many cancer patients, was also shown to be associated with an increased risk of VTE.

Results from numerous studies have identified the presence of a central venous catheter (CVC) as a risk factor for development of an upper-extremity DVT (UEDVT), although discrepancies exist concerning the incidence of catheter-related DVT. The association between catheter placement and development of DVT may be the result of venous stasis and vessel injury after insertion of the CVC or infections occurring as a result of catheter placement. Possible reasons for the reported discrepancies in the incidence of catheter-related DVT may include recent improvements in catheter materials and design and the different methods of diagnosing catheter-related DVT used in some of the studies (i.e., clinical, which are symptomatic, versus radiologic, which could be symptomatic or asymptomatic, diagnoses).
Not surprisingly, VTE risk was shown to increase with the number of VTE risk factors. Several VTE risk assessment scoring systems are in existence in which individual VTE risk factors are assigned weighted scores based on the level of VTE risk associated with that factor. For example, in one system a patient’s cumulative VTE risk score is determined by counting the number of VTE risk factors and calculating the sum of the associated weighted scores. A representative scoring system is not currently included in this version of the guidelines; however, these scoring systems can be incorporated to validate the use of thromboprophylaxis in all adult inpatients with cancer without contraindications to such therapy.

Diagnosis and Evaluation of VTE in Cancer Patients

DVT

Classic clinical symptoms (e.g., pain, unilateral edema and heaviness in the extremity distal to the site of the venous thrombosis, or edema in the supraclavicular space) are not present in all cases of acute DVT. Diagnosis of DVT in adults with cancer is facilitated by an increased level of clinical suspicion on presentation of any clinically-overt signs/symptoms of acute DVT (see DVT-1; DVT-2; DVT-3).

D-dimer testing is not recommended for the diagnosis of DVT in cancer patients because of its low specificity in this population and issues related to D-dimer assay variability.

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

In cases of negative or indeterminate ultrasound results and a continued high clinical suspicion of DVT, other imaging modalities (listed in order of preference) are recommended. 1) Contrast-enhanced computed tomography (CT) (i.e. indirect CT venography) is reportedly as accurate as ultrasonography in diagnosing femoropopliteal DVT and provides accurate imaging of the large pelvic veins and IVC. However, this method requires relatively high concentrations of contrast agent. 2) Magnetic resonance imaging (MRI; MR venography) provides a sensitive and specific evaluation of the pelvic veins and vena cava without the need for nephrotoxic contrast agents. Drawbacks to this method include higher cost. 3) Standard invasive venography, once considered the gold standard for DVT diagnosis, has largely been replaced by less invasive methods.
Few studies of UEDVT have been performed.\textsuperscript{45,48,67-70} Although UEDVT is frequently related to the presence of a catheter\textsuperscript{45,46,68,69} and associated with catheter malfunction,\textsuperscript{48} 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.\textsuperscript{45} However, in one study, only 50\% of isolated flow abnormalities in the upper extremity were related to the presence of DVT.\textsuperscript{67} A CT venogram may provide a more accurate assessment in cases of isolated flow abnormalities associated with an upper extremity. Invasive venography for the detection of UEDVT should be performed through a peripheral vessel in the extremity, although vein access may be limited by edema.\textsuperscript{68}

The panel recommends that patients diagnosed with calf and UEDVT who have relative contraindications to anticoagulation therapy be re-evaluated clinically for clot progression at 1 week after initial diagnosis. Imaging should then be repeated as clinically indicated. Similarly, patients with catheter-related DVT and central/proximal DVT should undergo follow-up imaging as clinically indicated. Reassessments of relative contraindications to anticoagulant therapy should accompany imaging evaluations (see DVT-2; DVT-3).

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

**Superficial Thrombophlebitis**

Diagnosis of superficial thrombophlebitis is made primarily on the basis of clinical symptoms (e.g., tenderness, erythema; possible indurated cord associated with superficial vein) and a negative ultrasound finding for DVT (see DVT-1). Progression of symptoms should be accompanied by follow-up imaging evaluation.

**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 (see PE-1; PE-2). Classic clinical signs and/or symptoms (e.g., current or recent history of DVT, unexplained shortness of breath, chest pain, tachycardia, apprehension, tachypnea, syncope, and oxygen desaturation) are not characteristic of all cases of acute PE.

D-dimer testing is not recommended for the diagnosis of PE in cancer patients because of its low specificity in this population\textsuperscript{52-54} and issues related to D-dimer assay variability.\textsuperscript{55,56}

Neither a chest radiograph nor an EKG of a patient with suspected PE is sensitive or specific enough to diagnose PE. However, a chest radiograph facilitates the diagnosis of comorbidities and conditions with clinically similar presentations and is useful in the interpretation of a ventilation-perfusion (V-Q) lung scan.\textsuperscript{71} The EKG provides information about existing cardiac disease and PE-related changes. Furthermore, EKG patterns characteristic of right-ventricular (RV) strain have been
associated with PE, and inverted T waves in precordial leads may be evident in cases of massive PE.

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

Alternative imaging modalities for the diagnosis of PE include 1) V-Q lung scan and 2) conventional pulmonary angiography. A V-Q scan is associated with less radiation exposure than CTPA, is useful for patients with renal insufficiency or contrast allergies, and is less invasive than conventional pulmonary angiography. A normal V-Q scan result essentially excludes PE. Elderly patients are more likely than younger patients to be diagnosed with an intermediate probability V-Q scan result. Both intermediate and low-probability V-Q scan results lack diagnostic utility and should be considered indeterminate. Further diagnostic testing should be performed if indicated clinically. In the face of clinical pulmonary embolus, a high-probability V-Q scan does not warrant further documentation before initiating treatment. Invasive conventional pulmonary angiography (direct pulmonary angiography), considered at one time to be the gold standard for diagnosing PE, is infrequently used today. Rarely, this method is combined with clot extraction or thrombolytic therapy. These measures should be planned before and executed simultaneously with conventional pulmonary angiography.

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

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

**Risks and Relative Contraindications Associated with Anticoagulation in Cancer Patients**

**Relative Contraindications to Anticoagulation**

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

Patients with a recent history of bleeding associated with the central nervous system or a spinal lesion are at increased risk of anticoagulant-associated bleeding. Package inserts for all 3 of the low molecular weight heparins (LMWHs) and fondaparinux include boxed warnings specifying that the risk of spinal or epidural hematoma resulting in long-term paralysis is increased when these anticoagulants are administered to patients receiving epidural or spinal anesthesia or those undergoing spinal puncture. Unfractionated heparin (UFH) should be also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture. Other factors, such as a patient’s risk of falling, should also be considered before anticoagulation therapy is ordered.

Prolonged aPTT is not considered a relative contraindication to anticoagulation therapy in patients with lupus inhibitors or anticoagulants. Lupus anticoagulants elevate the aPTT by interfering with phospholipid surfaces involved in coagulation. Antiphospholipid antibodies have been associated with an increased risk of VTE. Any patient who has experienced a thrombotic event and fulfilled diagnostic criteria for antiphospholipid syndrome should be considered for indefinite anticoagulation therapy.

**Risks Associated with Anticoagulation Therapy**

The use of anticoagulant agents in cancer patients is complicated by the fact that these patients have higher risks of both recurrent VTE and bleeding. In one prospective follow-up study of patients undergoing anticoagulation therapy, the 12-month cumulative incidences of major bleeding were 12.4% and 4.9% in patients with and without cancer, respectively (hazard ratio, 2.2; 95% CI, 1.2–4.1). In this study, one third of all cases of major bleeding occurred in the 5 to 10 days of initial heparinization, and the risk of bleeding increased with the extent of cancer.

In a randomized, controlled study of cancer patients receiving 3 months of either warfarin or enoxaparin therapy for the treatment of VTE, a higher bleeding rate was associated with warfarin therapy. Similarly, in another randomized trial, significantly increased bleeding rates (P = 0.01) were seen in patients receiving long-term (3-month) VTE treatment with warfarin when compared with patients receiving
tinzaparin therapy for the same duration. However, only a subset of this study population had been diagnosed with cancer, and bleeding rates in the population with cancer were not reported. Results of a retrospective evaluation indicated that bleeding complications were increased in cancer patients receiving therapy with oral vitamin K antagonists who had international normalized ratio (INR) values within the therapeutic range when compared with patients without cancer undergoing the same treatment. These results suggest that the INR may not be a good indicator of the likelihood of bleeding in cancer patients receiving oral anticoagulation therapy. In addition, an independent association of an INR greater than 6.0 and advanced malignancy was determined from results of a case-control study of patients receiving more than 1 month of warfarin therapy. However, results of a prospective cohort study of patients receiving long-term warfarin therapy for the treatment of VTE did not show significant differences between rates of major hemorrhage in patients with and without cancer.

Other risks associated with long-term use of anticoagulant agents include osteoporosis and heparin-induced thrombocytopenia (HIT) for patients receiving heparin-based drugs (For HIT, see section on Related Issues in VTE Prophylaxis and Treatment), and drug and food interactions for patients receiving oral anticoagulants. For example, decreases in bone mineral density of 1.8% and 2.6% and 3.1% and 4.8%, at 1 and 2 years of follow-up, were seen in patients who underwent long-term anticoagulant therapy for 3 to 24 months with an oral anticoagulant or enoxaparin, respectively. Warfarin has a very narrow therapeutic window, and its activity is known to be affected by the administration of many other drugs. For example, a number of antibiotics, including ciprofloxacin and metronidazole, potentiate the effect of warfarin, whereas other antibiotics such as dicloxacillin antagonize the effect of warfarin. Furthermore, certain chemotherapeutic agents such as the fluoropyrimidines (e.g., 5-fluorouracil and capecitabine) are known to increase the INR in patients undergoing anticoagulation with warfarin, and drug interactions between warfarin and certain selective estrogen receptor modulators (e.g., tamoxifen and raloxifene) have also been reported. Dietary intake of vitamin K and certain dietary supplements can also influence the effects of warfarin. Finally, acetaminophen, found in many medications, can increase the therapeutic effects of warfarin.

**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. Results from this study showed that treatment with heparin followed by warfarin dramatically reduced VTE recurrence and associated mortality in patients with symptoms of acute PE. Although most of the subsequent clinical trials evaluating the use of anticoagulation therapy in the prevention and treatment of VTE have not been placebo-controlled, the evidence supporting the effectiveness of such therapies is strong. Clinical evidence for the safety and efficacy of anticoagulation therapy in cancer patients is described later (see sections on VTE Prophylaxis and VTE Treatment). It is the directive of
the NCCN that all adult, hospitalized patients with cancer receive anticoagulation therapy in the absence of contraindications (category 1).

**Anticoagulation Agents**

Table 1 summarizes the anticoagulation agents used in the prophylaxis and/or treatment of VTE that are included in the guidelines (see VTE-C; VTE-D) and describes applying these therapies according to guideline recommendations. Food and Drug Administration (FDA) indications for each of these therapies are listed in the NCCN Venous Thromboembolic Disease Drugs & Biologics Compendium (for the latest version of the compendium, please visit [www.nccn.org](http://www.nccn.org)). The panel recommends that agent selection be based on criteria such as presence of renal failure; FDA approval; cost; ease of administration; need for monitoring of response; and ability to reverse anticoagulation. Suggested dosing schedules included in Table 1 were established according to NCCN VTE guidelines panel consensus and follow, in most cases, 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.70,108 (http://www.chestjournal.org/cgi/content/full/126/3_suppl/338S; http://www.chestjournal.org/cgi/reprint/126/3_suppl/401S).

**Low-molecular weight heparins**

LMWHs such as dalteparin, enoxaparin, and tinzaparin offer advantages of outpatient treatment and eliminate the need to monitor anticoagulant response for most patients. Although the 3 LMWHs are commonly considered equivalent agents that can be 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.109 However, recent results from a randomized clinical study comparing tinzaparin to dalteparin in the treatment of DVT and PE in 254 patients with active cancer or idiopathic VTE support the suggestions that these 2 drugs are equivalent in efficacy (recurrence of VTE) and safety.110 Enoxaparin88 is approved by the FDA for both prophylaxis and immediate treatment of VTE; dalteparin89 and tinzaparin87 are currently approved only for VTE prophylaxis and immediate VTE treatment, respectively. NCCN recommended dosing regimens for dalteparin in immediate VTE treatment and tinzaparin in VTE prophylaxis are based on results of clinical studies and panel consensus (see VTE-C; VTE-D; Table 1).110-115 Long-term anticoagulation therapy with a LMWH may require dosage reduction after an initial period. For example, in the CLOT study, the dalteparin dosing was lowered from 200 units/kg every day to 150 units/kg every day after 1 month.111 Only limited evidence exists concerning the safety and efficacy of LMWHs in special populations such as patients with renal insufficiency, obese patients (patients with a body mass index > 30 kg/m²), patients weighing < 50 kg, elderly patients (≥ 70 years), and patients with cancer.116-118 Of the 3 LMWHs, specific dosing recommendations for patients with severe renal insufficiency (creatinine clearance [Ccr] < mL/min) are available for enoxaparin only.88,119 Manufacturer recommendations specify 30 mg enoxaparin subcutaneous daily for VTE prophylaxis and 1mg/kg subcutaneous every 24 hours for VTE...
treatment for patients with \( C_{cr} \) less than 30 mL/min. In a recent study, renal clearance of enoxaparin was shown to be reduced by 31% and 44% in patients with moderate and severe renal impairment, respectively, leading the authors to suggest dosage reductions for patients with \( C_{cr} \) values less than 50 mL/min.\(^{120}\) Furthermore, some evidence supports downward dose adjustments of LMWH in the management of patients with \( C_{cr} \) of 30 to 60 mL/min.\(^{121,122}\)

The panel currently recommends caution when using any LMWH in patients with severe renal insufficiency and that manufacturer specifications be followed when administering enoxaparin to these patients.\(^{88}\) Only limited data are available with respect to the safety of dalteparin and tinzaparin in this population. The panel also recognizes current evidence suggesting caution also be used when administering LMWHs to patients with \( C_{cr} \) less than 50 mL/min. The issue of LMWH dosage adjustments in populations with renal insufficiency will be re-evaluated in the 2007 version of the guidelines.

Concerns also exist with respect to maintaining and monitoring therapeutic concentrations of anticoagulants in obese patients. In one study, thromboprophylaxis with 5000 units of dalteparin per day was ineffective in reducing the incidence of symptomatic VTE and asymptomatic DVT in patients with a body mass index of 40 kg/m\(^2\) or greater.\(^{123}\) Hospitalization of morbidly obese cancer patients with administration of UFH should be considered. The panel suggests that each institution prepare a LMWH dosing algorithm tailored for obese patients. Because only limited data are available for the use of LMWHs in patients weighting less than 50 kg,\(^{87-89}\) the panel also recommends caution when using these agents in patients with low body weight and in elderly patients. LMWHs are contraindicated in patients with HIT and should only be used with extreme caution in patients with a history of HIT (see section on Related Issues in VTE Prophylaxis and Treatment). Later sections summarize the clinical evidence for the safety and efficacy of LMWHs in cancer patients (see sections on VTE Prophylaxis and VTE Treatment).

**Pentasaccharide-Specific Inhibitor of Factor Xa**
Fondaparinux is the only pentasaccharide approved by the FDA for the prophylaxis and treatment of VTE.\(^{86}\) Advantages of fondaparinux in the treatment of VTE include specific neutralization of Factor Xa, elimination of the need to monitor anticoagulant response in most patients, and lack of cross reactivity with the antibody associated with HIT.\(^{86,124-127}\) However, the use of fondaparinux in patient populations with renal insufficiency, obesity,\(^{118}\) or HIT\(^{125}\) has not been well defined, although there is some evidence to support its safe and effective use for VTE prophylaxis for older patients with a broad range of body weights.\(^{122}\) Pharmacologic characteristics of fondaparinux include renal elimination and a very long half-life of 17 to 21 hours.\(^{86}\) Prescribing information for fondaparinux provided by the manufacturer specifies that the drug is contraindicated in patients with severe renal insufficiency (\( C_{cr} < 30 \) mL/min) and for thromboprophylaxis in patients weighing less than 50kg undergoing orthopedic or abdominal surgery. It should be used with caution in elderly patients and individuals with moderate renal insufficiency (\( C_{cr} < 50 \) mL/min).\(^{86}\) The NCCN panel recommends against the use of fondaparinux in patients with severe renal insufficiency and advises caution when using fondaparinux in all patients weighing < 50kg, patients with renal dysfunction, and elderly patients.
Unfractionated Heparin
UFH for use in the prophylaxis of VTE is administered subcutaneously (low-dose heparin), but intravenous heparin is indicated to treat VTE (see Table 1). Low-dose UFH (5000 units) administered 3 times a day (every 8 hours) was shown to be more effective than low-dose UFH administered twice a day in preventing DVT in general surgery patients and is the regimen recommended by the panel for the prophylaxis of VTE in cancer patients. Initial dosing of UFH in the treatment of VTE is weight based, with a recommended regimen of 80 units/kg load followed by 18 U/kg per hour infusion. Patients receiving UFH must initially be hospitalized and monitored for anticoagulant response. The panel recommends UFH as the agent of choice in patients with Cr less than 30 mL/min, because the liver is a main site of heparin biotransformation. 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 (see section on Related Issues in VTE Prophylaxis and Treatment).

Warfarin
Warfarin is an option for cancer patients with VTE. Initially, when warfarin is the choice for chronic anticoagulation, it should be administered concomitantly with UFH, LMWH, or fondaparinux, except when treating HIT where warfarin administration is initially overlapped with administration of a DTI (see section on Related Issues in VTE Prophylaxis and Treatment). Daily and then frequent (at least weekly) monitoring of the INR is required. Warfarin can be safely administered to patients with renal insufficiency, although response to warfarin may be potentiated in patients with hepatic insufficiency.

Direct Thrombin Inhibitors
Direct thrombin inhibitors (DTIs) are discussed in a later section (see section on Related Issues of VTE Prophylaxis and Treatment).

Mechanical Devices
Sequential compression devices
One of the main advantages of sequential compression devices (SCDs) is absence of associated bleeding risk. However, disadvantages include the potential for interference with ambulation and the need to keep devices in place nearly continuously.

Vena Cava Filters
Placement of a vena cava filter has the main advantage of preventing PE in patients at high risk of VTE and those with VTE who have contraindications to anticoagulant therapy (see VTE-F). However, placement of an IVC filter does not prevent DVT and has been associated with an increased risk of recurrent DVT in some studies. Only one randomized, controlled trial has been conducted on the efficacy and safety of IVC filters compared with anticoagulant therapy.

VTE Prophylaxis
Mechanical Prophylaxis
Mechanical prophylaxis with SCDs is recommended by the panel for all hospitalized patients with a diagnosis of cancer, regardless of perceived risk of bleeding (see VTE-1). SCDs should be used concomitantly with anticoagulation therapy in the absence of high
bleeding risk or without anticoagulation therapy in patients with one or more contraindications to such therapy. Steps should be taken to ensure the continuous application of SCDs. These devices should be used with caution in patients with open wounds or arterial insufficiency. Graduated compression stockings, used to maintain venous compression, are not a substitute for SCDs.

The use of SCDs has been less well studied than the use of anticoagulation therapy in VTE prevention. Most of the data on the effectiveness of mechanical prophylaxis have come from the surgical population. For example, in a study comparing VTE rate in gynecologic oncology surgery patients receiving either low-dose heparin 3 times a day (starting with the day before surgery and continuing for 7 days or longer after surgery) or intermittent pneumatic calf compression, no difference was seen between the 2 groups. A retrospective evaluation of high-risk colorectal surgery patients who had received mechanical prophylaxis without anticoagulant therapy indicated that SCDs were effective in preventing postoperative VTE. However, results from a recent retrospective study of 839 patients over a 2-year period who had undergone abdominal surgery for gynecologic cancers and received pneumatic compression and early ambulation for VTE prophylaxis showed that the incidence of PE in cancer patients (4.1%) exceeded by 14-fold the incidence of PE in patients with benign disease (0.3%).

Prophylactic Anticoagulation Therapy
The panel recommends prophylactic anticoagulation therapy for all inpatients with a diagnosis of active cancer (or for whom clinical suspicion of cancer exists) who do not have a contraindication to such therapy (category 1; see VTE-1; VTE-C). This recommendation is based on an assumption that ambulation in hospitalized cancer patients is inadequate to reduce VTE risk. Recommended anticoagulant options for VTE prophylaxis of cancer patients are listed in Table 1. Anticoagulation therapy should be administered throughout hospitalization. Continuation of VTE prophylaxis after hospital discharge should be strongly considered in high-risk cancer patients (e.g., after cancer surgery).

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

For preventing VTE associated with a CVC, no difference in CVC-related VTE rate was seen between cancer patients undergoing prophylaxis with enoxaparin for 6 weeks and those receiving placebo in a double-blind, randomized study. Therefore, the panel does not recommend VTE prophylaxis for patients with a CVC.
VTE Treatment

Upon diagnosis of VTE, the panel recommends beginning immediate treatment (5-7 day duration) with either UFH (IV), LMWH, or in some cases, fondaparinux in cancer patients without contraindications to anticoagulation. Immediate treatment should be followed by long-term (3-6 months for DVT and 6-12 months for PE) treatment with either a LMWH or warfarin (see Table 1 and DVT-2; DVT-3; PE-2; VTE-D). Anticoagulation for an indefinite duration should be considered in patients with active cancer or persistent risk factors. If warfarin is used for long-term treatment, it should be administered at the start of therapy concomitantly with the agent used for immediate treatment. LMWH as monotherapy (without warfarin) is recommended for long-term (up to 6 months) treatment of proximal DVT or PE, and prevention of recurrent VTE in patients with advanced or metastatic cancer who do not have contraindications to anticoagulation. However, issues such as patient preference and cost should also be considered. IVC filter placement should be considered for patients with lower-extremity (e.g., calf) DVT characterized as progressive, central/proximal DVT, or PE who have contraindications to anticoagulation, PE while on adequate anticoagulation for DVT, or new PE while on adequate anticoagulation for PE. Placement of an IVC filter should also be considered for patients who are non-adherent with prescribed anticoagulation, those with baseline pulmonary dysfunction severe enough to make any new or recurrent PE life threatening, and those with documented multiple PE and chronic pulmonary hypertension (see VTE-F).

Immediate VTE Treatment

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

Long-Term VTE Treatment

Several studies evaluating the efficacy and safety of different anticoagulant regimens in the long-term treatment of VTE in patients with cancer have been performed. In one randomized, open-label trial (The CANTHANOX trial), the use of long-term (3 months) enoxaparin versus long-term warfarin was evaluated after immediate treatment with
either LMWH or UFH in the treatment of 146 cancer patients with VTE. The primary endpoint of this study was a combined outcome event including major bleeding and recurrent VTE. In the groups receiving long-term enoxaparin and warfarin, 10.5% and 21.1% of patients, respectively, experienced either major bleeding or recurrent VTE (P = 0.09) within 3 months. Although the differences between the 2 treatment groups were not statistically significant, most were associated with an increase in bleeding in the group receiving warfarin.

The randomized, multicenter LITE study evaluating the use of long-term (84 days) tinzaparin versus immediate (5 days) UFH followed by long-term (84 days) warfarin therapy in high-risk patients with VTE reported no significant differences in VTE recurrence rates between the 2 groups overall or between the 2 groups within the subset of 206 patients with cancer. However, bleeding complications were significantly higher for the overall group receiving warfarin therapy. Finally, the CLOT trial compared the efficacy and safety of immediate (5–7 days) dalteparin followed by long-term (6 months) therapy with an oral coumarin derivative with long-term dalteparin therapy in patients with cancer, the majority of which had metastatic disease, after diagnosis of acute proximal DVT, PE, or both. This study showed probabilities of recurrent VTE at 6 months of 17% and 9% in cancer patients receiving oral anticoagulants and dalteparin, respectively. No difference in bleeding or PE rate was seen for the 2 groups. The results of this study support use of LMWHs as long-term anticoagulation therapy in patients with metastatic disease who are diagnosed with acute VTE. Some limitations of the CLOT study include the lack of patients with below-the-knee or catheter-related thrombosis, a study duration of only 6 months, that the efficacy difference was observed for development of recurrent DVT only (not PE), and uncertainty on whether these results can be extrapolated to LMWHs other than dalteparin.

Increased survival rates have been reported for subgroups of cancer patients receiving long-term treatment with dalteparin versus other VTE therapies or placebo. For example, although no survival differences were seen in groups of patients with advanced cancer without VTE receiving either dalteparin or placebo in the FAMOUS study, results from a subgroup analysis of patients with better prognoses suggested that 1-year survival rates were higher for patients receiving dalteparin compared with patients receiving placebo. A posthoc analysis of patients from the CLOT study also indicated that no differences in 1-year survival were seen between groups of patients with metastatic disease receiving either long-term dalteparin or oral coumarin derivatives, whereas 1-year survival rates were higher in the subgroup of patients without metastases receiving dalteparin when compared with patients in the same subgroup receiving oral VTE therapy. Additional evaluations of the putative anti-tumor effects of LMWHs are needed before recommendations pertaining to this issue can be made.

**Treatment of Catheter-Related DVT**

The central tenant guiding treatment of catheter-related DVT is concerned with whether the catheter is required (see DVT-3; VTE-D). Catheter removal is recommended in the case of catheter-related DVT when the catheter is not required or when the catheter is required but relative contraindications to anticoagulation therapy exist. Anticoagulation therapy is recommended while the catheter is in place (in the absence of contraindications) and for 1 to 3 months after
catheter removal. If the catheter is required but DVT symptoms persist or a clot continues after anticoagulation therapy is started, the panel recommends that the catheter be removed. Patients with catheter-related DVT and relative contraindications to anticoagulation therapy should be followed up for changes in these contraindications as clinically indicated; anticoagulation therapy is recommended after contraindications are resolved.

No randomized, controlled trials have been reported evaluating the effects of particular therapeutic strategies on outcomes of CVC-associated VTE. A recent prospective study of 444 cancer patients with CVC showed an incidence of symptomatic catheter-related DVT of 4.3%. Of 19 patients with catheter-related DVT, 9 were treated with anticoagulation therapy only, 8 patients underwent anticoagulation therapy and catheter removal, 1 patient was treated with catheter removal only, and 1 patient did not receive any treatment. The duration of anticoagulation therapy was not specified, but evaluation of the 15 patients alive at 24 weeks after diagnosis of catheter-related DVT revealed that residual symptoms of DVT were present in only 2.

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

Treatment of PE
A high-risk patient with PE is defined as a cancer patient with acute PE and abnormal results of risk-stratifying evaluations (e.g., serum cardiac troponin levels and RV function) performed on hospital admission (see PE-2). This population includes hemodynamically unstable patients with imaging evidence of massive PE and stable patients with submassive PE and evidence of moderate or severe RV dysfunction.

In patients without relative contraindications to anticoagulation, immediate anticoagulation therapy should be started at PE diagnosis; evaluation of risk should be performed concurrently with PE diagnosis or as soon as relevant data are available. After considering the cancer status of the high-risk patient with PE, the physician should consider the use of thrombolytic therapy and/or pulmonary embolectomy along with a concomitant evaluation of the patient’s risk of bleeding. In addition, an IVC filter should be considered for this patient population.

A meta-analysis of 9 randomized, controlled clinical studies of unselected patients with acute PE did not show thrombolytic therapy to be superior to anticoagulation therapy with intravenous heparin for reducing mortality or PE recurrence, and it was associated with an increased bleeding risk. Another meta-analysis of the same 9 clinical trials indicated that patients receiving thrombolytic therapy were less likely to experience a composite endpoint of recurrence of PE/death than patients receiving IV heparin. However, the difference in PE recurrence rates alone was not statistically significant, and bleeding risk was found to be elevated in the patients receiving thrombolytic therapy.
No differences in in-hospital mortality were observed in the randomized, placebo-controlled MAPPET-3 trial of hemodynamically stable patients with submassive acute PE and pulmonary hypertension or evidence of RV dysfunction who received heparin in conjunction with alteplase or heparin plus placebo for 2 hours. However, treatment escalation because of clinical instability was significantly increased in the latter group.\textsuperscript{156} Reports from several recent studies evaluating the use of pulmonary embolectomy in patients with acute PE provide support for the use of this procedure in patients with hemodynamically stable or unstable acute PE characterized by RV dysfunction.\textsuperscript{157-159} An important consideration for these guidelines is that none of these studies evaluating the use of thrombolytic therapy or surgical embolectomy to treat patients with acute PE specifically address treating cancer patients.

Although the ACCP recommends against the use of thrombolytic therapy or pulmonary embolectomy in most patients with PE, they suggest using thrombolytic therapy in selected patients, such as those with massive PE who are hemodynamically unstable and without a high risk of bleeding. The ACCP suggests the use of pulmonary embolectomy for selected patients with critical status who are unable to undergo thrombolytic therapy due to an emergent situation.\textsuperscript{70}

**Treatment of Superficial Thrombophlebitis**

Anti-inflammatory medications, warm compresses, and elevation of the affected limb are recommended for the initial treatment of superficial thrombophlebitis (see DVT-1; VTE-D). Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients with platelet counts less than 20,000 to 50,000/mcL or with severe platelet dysfunction. Anti-inflammatory agents are recommended for the symptomatic treatment of superficial thrombophlebitis only, not for DVT prophylaxis.

Only a limited number of studies have evaluated the clinical significance of superficial thrombophlebitis, its associated progression to VTE, and the effect of anticoagulant agents on its course.\textsuperscript{160, 161} In a prospective assessment of 60 consecutive patients with superficial thrombophlebitis of the greater saphenous vein, the combined incidence of DVT and superficial thrombophlebitic events over a 6-month follow-up period was lower in patients treated with twice daily subcutaneous injections of high-dose heparin (12,500 IU for 1 week, followed by 10,000 IU) for 4 weeks when compared with patients receiving 4 weeks of low-dose (5000 IU) heparin therapy.\textsuperscript{162} A pilot study evaluating the effects of once daily administration of an LMWH, an NSAID, or placebo for 8 to 12 days on the clinical course of superficial thrombophlebitis showed no significant differences between treatment and placebo groups with respect to progression to DVT.\textsuperscript{163} However, all active treatments reduced the combined rate of DVT and superficial thrombophlebitis compared with placebo, although no significant differences were observed between active treatment groups. This possibly indicates that longer treatment durations may be required.

Therefore, prophylactic anticoagulation is not recommended by the panel in cases of uncomplicated, self-limited superficial thrombophlebitis. Anticoagulation therapy (e.g. intravenous UFH or a LMWH for at least 4 weeks) should be considered for patients with superficial thrombophlebitis characterized by symptom progression.
Anticoagulation with warfarin therapy is also an option after immediate treatment.

**VTE Therapies: Response Assessment**

Intensive monitoring of the effects of some of the anticoagulant agents on clotting potential is particularly important in patients with cancer (see [VTE-D]). The recommendations on monitoring anticoagulant response included in the NCCN VTE guidelines may be superseded by written SOPs specific to an institution.

**UFH**

Heparins indirectly affect the blood clotting system by potentiating antithrombin, thereby facilitating inhibition of thrombin, factor Xa, and, to a lesser extent, several other blood clotting factors. The aPTT provides an evaluation of the overall ability of the intrinsic and common blood clotting pathways to function and is particularly sensitive to agents that inhibit thrombin. Therefore, the efficacy and safety of UFH in the treatment of VTE is most commonly evaluated by determining the aPTT and depends on the establishment of an optimal aPTT range. A fixed aPTT therapeutic range of 2.0 to 2.9 times the control value (i.e., the baseline aPTT for the patient) is recommended by the panel when UFH is administered. Regular calibration of an aPTT therapeutic range against heparin levels of 0.3 to 0.7 IU/mL (as determined by anti-factor Xa chromogenic assay) as recommended by the College of American Pathologists (CAP) and ACCP is advised. Because of the low risk of an exaggerated anticoagulant response, monitoring is not typically performed after administration of prophylactic subcutaneous UFH.

**LMWHs and Pentasaccharide (Fondaparinux)**

LMWHs act by potentiating the inhibitory activity of antithrombin against factor Xa and to a lesser extent, thrombin. Fondaparinux is a synthetic indirect Xa inhibitor that also functions through potentiation of antithrombin inhibition. Measurement of factor Xa inhibition, not aPTT, is necessary to evaluate the effect of LMWH or fondaparinux on clotting potential, because thrombin inhibition associated with LMWH or fondaparinux is weak or absent, respectively. However, only limited data are available on the use of factor Xa levels to monitor and adjust LMWH or fondaparinux therapy, and monitoring of patients receiving LMWH or fondaparinux is generally not performed because of the more predictable dose response associated with these agents. In general, the panel recommends limiting the use of LMWHs and fondaparinux in patients with renal insufficiency and those at extremes of body weight (as described previously), rather than close monitoring. Panel opinions diverged on the utility of measuring factor Xa inhibition in certain cases, such as in patients with very high body weight (> 150 kg) receiving LMWH for an extended period of time.

**DTIs**

Lepirudin, argatroban, and bivalirudin are direct inhibitors of thrombin. Therefore, the effect of these agents on clotting potential can be evaluated through measurement of the aPTT, although results can be affected by the specific DTI and the aPTT assay reagents used. Target aPTT ranges of 1.5 to 2.0 times control, 1.5 to 3.0 times control and 1.5 to 2.5 times control are recommended when using lepirudin, argatroban, and bivalirudin, respectively. The aPTT range of 1.5 to 2.0 times control for lepirudin is lower than specified by the manufacturer.
Recent studies have shown that accumulation of this agent may occur in patients with even mild renal impairment, thereby necessitating more frequent aPTT monitoring and a lower target aPTT range.167,168

**Warfarin**

Dosing of warfarin can be highly variable, and close monitoring of the INR (ratio of PT to the mean normal PT), which provides an assessment of the extrinsic and common blood clotting pathways, is required to determine the therapeutic warfarin dose for an individual patient164 (see section on Risks/Relative Contraindications Associated with Anticoagulation in Cancer Patients). The panel recommends a target INR of 2.5 (range, 2.0–3.0) for VTE treatment; this range is consistent with ACCP recommendations.70 Care should be used when making the transition from a DTI to warfarin in the management of HIT, because all of the DTIs (argatroban, in particular) prolong the INR.164,169 (see section on Related Issues in VTE Prophylaxis and Treatment).

**Reversal of Anticoagulant Activity**

The anticoagulant effects of UFH are fully reversible with protamine sulfate, and LMWHs are partially antagonized by protamine sulfate, although this agent must be used with caution because it can cause severe hypotension or anaphylactoid reactions.87-90,117 No available agents act to directly reverse the activities of specific inhibitors of factor Xa or thrombin, although intravenous recombinant human factor VIIa can be administered to help reverse the effects of LMWHs, DTIs, and fondaparinux. In many cases, the effects of warfarin can be reversed through administration of oral vitamin K.131 Alternatives with the ability to rapidly reverse warfarin-related effects include intravenous vitamin K, fresh-frozen plasma, and coagulation factor concentrates. These are used to reverse serious or life-threatening bleeding and in the rapid preparation of patients for invasive procedures associated with bleeding risk.

**Related Issues in VTE Prophylaxis and Treatment**

**Diagnosis and Management of HIT**

Specific guideline recommendations regarding HIT are available from the ACCP (http://www.chestjournal.org/cgi/content/full/126/3_s suppl/311S).125 HIT is caused by a relatively common immunologic reaction to heparin-based products (see VTE-G). 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.171 In another study, 2.7% of patients treated with UFH developed HIT.172 Antibodies to platelet factor 4, formed following its complexion with heparin, result in thrombocytopenia, and, in certain cases, thrombosis after binding of immune complexes to platelet receptors and subsequent platelet/coagulation cascade activation.125,168 Clinical evidence of HIT can include formation of necrotic lesions at injection sites, arterial thromboembolic complications, and development of VTE.173,174 Most typically, HIT occurs after 4 to 14 days of exposure to heparin-based products or previous exposure to such agents within a 2 week period. Less common is rapid-onset HIT, occurring less than 2 days after initial administration of the heparin-based product, and delayed-onset HIT, which can occur days or weeks after heparin therapy has been discontinued.

Some evidence exists indicating that cancer patients are at increased risk of developing HIT and HIT-related VTE.175 HIT has been
associated with the use of both LMWHs and UFH. Increased rates of HIT have been observed in patients receiving heparin-based therapy who were previously exposed to such therapy. Results of some studies have indicated that the frequency of HIT with LMWH and UFH is similar, whereas other studies suggest a lower incidence of HIT in patients receiving LMWH relative to those receiving UFH.

The panel recommends platelet monitoring at baseline and then on a daily basis and every 3 to 5 days for 2 weeks in patients receiving anticoagulation therapy with UFH or a LMWH, respectively. Testing for the presence of HIT antibody should be started after a drop in platelet count by more than 50% or other clinical evidence of HIT (see VTE-G). The immediate management of HIT includes discontinuance of heparin-based products and administration of a DTI (see section on Anticoagulant agents for the treatment of HIT and Table 1 for dosing recommendations); these measures are recommended before obtaining results of HIT antibody testing if clinical suspicion of HIT is high. Platelets should not be transfused during an episode of HIT. Warfarin therapy should be initiated on platelet count recovery (e.g., >100,000-150,000/ mcL). After platelet recovery, warfarin should be overlapped with a DTI for at least 5 days and until the target INR is reached for at least 2 days, the platelet count has stabilized, and symptomatic thrombosis is controlled, at which point the DTI is discontinued. The panel recommends routine screening ultrasounds for patients with HIT, and warfarin therapy durations longer than 1 month in patients who experience asymptomatic DVT in association with HIT.

### Anticoagulant Agents for the Treatment of HIT

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

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

The panel recommends against the off-label use of fondaparinux to treat a current episode of HIT, but allows that it may be considered as a VTE prophylactic agent in patients with a history of HIT or to
treat patients who have recovered from a recent episode of HIT and who are not yet stable on warfarin therapy but ready to be discharged from the hospital (see section on VTE Therapies for the Prophylaxis and/or Treatment of VTE in Cancer Patients for additional recommendations on the use of fondaparinux).

Warfarin therapy in the treatment of HIT should not be initiated until after platelet count recovery because of the potential for skin necrosis and/or gangrene, which can occur because warfarin inhibits protein C in the setting of HIT thrombosis.186

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 (see VTE-E). The risks and probability of success of the interventions should be considered as well. Factors to consider before implementing anticoagulation therapy include the patient’s cancer status; possible patient refusal; lack of therapeutic advantage, if no oncologic intervention is planned; lack of palliative benefits; and whether anticoagulation is associated with an unreasonable burden. Likewise, careful consideration of these issues is also very important in deciding to withhold or withdraw VTE therapy.

Summary

Recognizing the increased risk of VTE in cancer patients is the first step in preventing the occurrence of VTE and promptly identifying VTE in these patients. The NCCN panel recommends VTE thromboprophylaxis for all hospitalized patients with cancer who do not have contraindications to such therapy, and the panel also emphasizes that an increased level of clinical suspicion of VTE should be maintained for cancer patients. Careful evaluation and follow-up of cancer patients in whom VTE is suspected and prompt treatment and follow-up for patients diagnosed with VTE is recommended after the cancer status of the patient and the risks and benefits of treatment are considered.

Future Directions

The following additional topics will be reviewed for the 2007 version of the NCCN VTE Guidelines:

1. Recommendations for VTE prevention and treatment in outpatients with cancer
   a. Long-term (outpatient) VTE prophylaxis
   b. Long-term (outpatient) VTE treatment
      • Discussion of possibility of indefinite treatment in patients with active cancer with history of VTE
      • Discussion of relative merits of warfarin and LMWHs as long-term (especially > 6 months) therapy
2. Organ-based thrombosis: intraabdominal and intrathoracic clots
3. Vena cava filters: temporary vs. permanent
4. Thrombolytic therapy in cancer patients with PE
   a. Effect on function
   b. Effect on mortality
   c. Morbidity associated with use
   d. Treatment of “massive” DVT
5. Additional stratification of cancer population
   a. Medical versus surgical patients
b. Pre- versus post-surgery patients  
c. Patients with renal insufficiency

6. Screening with a relative risk assessment tool  
7. Long-term surveillance  
8. Research questions
   a. Therapeutic success of VTE prophylaxis and treatment  
   b. Effects of introduction of NCCN VTE Guidelines on management of cancer patients

Disclosures for the NCCN Venous Thromboembolic Disease Guidelines Panel
At the beginning of each panel meeting to develop NCCN Guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers’ bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Amgen; Celgene; Eisai Pharmaceuticals, Inc; GlaxoSmithKline; Sanofi-Aventis; and Zycare. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
### Table 1
**Recommendations for Anticoagulant Use in Patients with Active Cancer: Applications, Dosages, and Duration of Therapy***

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Drug Class</th>
<th>VTE-Related Applications</th>
<th>Dosing for VTE Prophylaxis</th>
<th>Duration of VTE Prophylaxis</th>
<th>Dosing for VTE Treatment</th>
<th>Duration of VTE Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin (UFH)†</td>
<td>Antithrombin potentiator (thrombin and factor Xa inhibitor)</td>
<td>Prophylaxis and treatment</td>
<td>5000 units SC 3 times daily</td>
<td>Admission to hospital discharge‡</td>
<td>80 units/kg load, then 18 units/kg/hr; target aPTT 2.0-2.9 x control</td>
<td>Initial treatment§ to be followed by long-term// treatment with either warfarin (see below) or LMWH</td>
</tr>
<tr>
<td>Dalteparin†¶**</td>
<td>Antithrombin potentiator (factor Xa inhibitor with some thrombin inhibition)</td>
<td>Prophylaxis and treatment</td>
<td>5000 units SC daily</td>
<td>Admission to hospital discharge‡</td>
<td>200 units/kg SC daily††</td>
<td>Initial treatment§ to be followed by long-term// treatment with either warfarin (see below) or LMWH</td>
</tr>
<tr>
<td>Enoxaparin†¶**</td>
<td>Antithrombin potentiator (Factor Xa inhibitor with some thrombin inhibition)</td>
<td>Prophylaxis and Treatment</td>
<td>40 mg SC daily (30 mg SC daily in patients with Ccr &lt;30 mL/min)</td>
<td>Admission to hospital discharge‡</td>
<td>1.0 mg/kg SC every 12 hrs†† (1.0 mg/kg SC every 24 hrs in patients with Ccr &lt;30 mL/min)</td>
<td>Initial treatment§ to be followed by long-term// treatment with either warfarin (see below) or LMWH</td>
</tr>
<tr>
<td>Tinzaparin†¶**</td>
<td>Antithrombin Potentiator (Factor Xa inhibitor with some thrombin inhibition)</td>
<td>Prophylaxis and Treatment</td>
<td>4500 units SC daily or 75 U/kg SC daily</td>
<td>Admission to hospital discharge‡</td>
<td>175 U/kg SC daily††</td>
<td>Initial treatment§ to be followed by long-term// treatment with either warfarin (see below) or LMWH</td>
</tr>
<tr>
<td>Fondaparinux**‡‡</td>
<td>Specific Factor Xa Inhibitor</td>
<td>Prophylaxis and Treatment</td>
<td>2.5 mg SC daily</td>
<td>Admission to hospital discharge‡</td>
<td>Weight-based dosing: 5.0 mg (&lt;50 kg) -7.5 mg (50-100 kg) -10 mg (&gt;100 kg) SC daily</td>
<td>Initial treatment§ to be followed by long-term// treatment with either warfarin (see below) or LMWH</td>
</tr>
<tr>
<td>Warfarin§§</td>
<td>Vitamin K Antagonist</td>
<td>Treatment (long-term//)</td>
<td>NA</td>
<td>NA</td>
<td>Start at 2.5-5.0 mg/day; subsequent dosing based on INR value; target INR is 2.0-3.0</td>
<td>Long-term// treatment following initial§ UFH, LMWH, or fondaparinux therapy; long-term// following initial treatment for HIT</td>
</tr>
</tbody>
</table>

*Continued…*
### Venous Thromboembolic Disease

#### Anticoagulant Drug Class VTE-Related Applications

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Drug Class</th>
<th>VTE-Related Applications</th>
<th>Dosing for VTE Prophylaxis</th>
<th>Duration of VTE Prophylaxis</th>
<th>Dosing for VTE Treatment</th>
<th>Duration of VTE Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban/</td>
<td>Direct Thrombin</td>
<td>Treatment of HIT with (or without)</td>
<td>NA</td>
<td>NA</td>
<td>2.0 mcg/kg/min IV infusion; target aPTT 1.5-3.0 x control††</td>
<td>Initial treatment following discontinuation of heparin-based treatment in HIT – initiate warfarin upon platelet recovery - overlap DTI and warfarin for at least 5 days until target INR is reached.</td>
</tr>
<tr>
<td></td>
<td>Inhibitor</td>
<td>thrombosis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lepirudin***</td>
<td>Direct Thrombin</td>
<td>Treatment of HIT with (or without)</td>
<td>NA</td>
<td>NA</td>
<td>0.1 mg/kg/hr IV infusion; target 1.5-2.0 x control</td>
<td>Initial treatment following discontinuation of heparin-based treatment in HIT – initiate warfarin upon platelet recovery - overlap DTI and warfarin for at least 5 days until target INR is reached.</td>
</tr>
<tr>
<td></td>
<td>Inhibitor</td>
<td>thrombosis</td>
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<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Direct Thrombin</td>
<td>Treatment of HIT with (or without)</td>
<td>NA</td>
<td>NA</td>
<td>0.15-0.20mg/kg/hr continuous IV infusion (Lower doses may be required, especially in patients with organ dysfunction.); adjust to target aPTT (1.5-2.5 x control) 4-6 hours after each dose adjustment</td>
<td>Consider as initial treatment following discontinuation of heparin-based treatment in HIT – initiate warfarin upon platelet recovery - overlap DTI and warfarin for at least 5 days until target INR is reached.</td>
</tr>
<tr>
<td></td>
<td>Inhibitor</td>
<td>thrombosis†††</td>
<td></td>
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</tr>
</tbody>
</table>

*Dosages are listed according to package inserts of respective drugs with the exception of off-label uses and lepirudin dosing.
†Discontinue if HIT is present
‡Recommendations on duration of long-term outpatient prophylaxis to be included in 2007 version of NCCN VTE Guidelines.
§Immediate duration = 5–7 days.
// Long-term treatment duration is defined as 3-6 months for DVT and 6-12 months for PE (Consider continued treatment beyond these ranges if initial thrombotic event is spontaneous and/or as long as cancer remains active.)
¶LMWH
**Use with caution in patients with renal insufficiency;
††After acute treatment, lower doses may be used for long-term therapy.
‡‡Avoid in patients with severe renal insufficiency;
§§When used as long-term therapy, initiate warfarin concomitantly with initial therapy except in cases of HIT.
/////Avoid use in patients with hepatic failure
¶¶Initial dose for patients with moderate hepatic insufficiency is 0.5 mcg/kg/min IV infusion according to package insert.
***Avoid use in patients with renal insufficiency.
†††Off-label for the treatment of HIT.
References


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139. Brender E. Use of emboli-blocking filters increases, but rigorous data are lacking. JAMA. 2006;295:989-990.


