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Venous Thromboembolic Disease

Clinical Practice Guidelines in Oncology

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Abstract

Venous thromboembolism (VTE) remains a common and life-threatening complication among patients with cancer. Thromboprophylaxis can be used to prevent the occurrence of VTE in patients with cancer who are considered at high risk for developing this complication. Therefore, it is critical to recognize the various risk factors for VTE in patients with cancer. Risk assessment tools are available to help identify patients for whom discussions regarding the potential benefits and risks of thromboprophylaxis would be appropriate. The NCCN Clinical Practice Guidelines in Oncology for VTE provide recommendations on risk evaluation, diagnosis, prevention, and treatment of VTE in patients with cancer. (*JNCCN* 2013;11:1402–1429)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise 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.

Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in patients with cancer.[1,2] Results from a retrospective study of hospitalized adult patients with cancer with neutropenia (N=66,106) showed that approximately 3% to 12% of these patients, depending on the type of malignancy, experienced VTE during their first hospitalization.[1] In a recent health claims database analysis of patients undergoing chemotherapy for solid tumors in the ambulatory setting (N=17,284), VTE

Please Note

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Disclosures for the NCCN Venous Thromboembolic Disease Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Venous Thromboembolic Disease Panel members can be found on page 1429. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

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

occurred in 12.6% of patients during the 12-month period from initiation of chemotherapy.[3] The incidence ranged from 8% to 19%, depending on the tumor type. VTE incidence was 1.4% among age- and gender-matched control cohorts without cancer.[3] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for VTE specifically outline strategies to prevent and treat VTE in adult patients with either a diagnosis of cancer or for whom cancer is clinically suspected.

In the NCCN Guidelines, VTE is broadly defined to include deep venous thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT), and thrombosis in other vascular territories (eg, portal vein, mesenteric vein, inferior and superior vena cava, femoral veins). DVT management is divided into 5 categories in this document, which differ in terms of associated morbidity, treatment, and long-term effects. These categories include the upper extremity and the superior vena cava (SVC); the lower extremity, including the inferior vena cava (IVC), pelvis, iliac, femoral, and popliteal veins; the distal lower extremity (eg, calf); the 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.[4,5] Pathophysiologic explanations of the cause of VTE in cancer include known hypercoagulability (eg, procoagulants, such as tissue factor expressed by cancer cells), vessel wall damage, and stasis from

Text cont. on page 1411.

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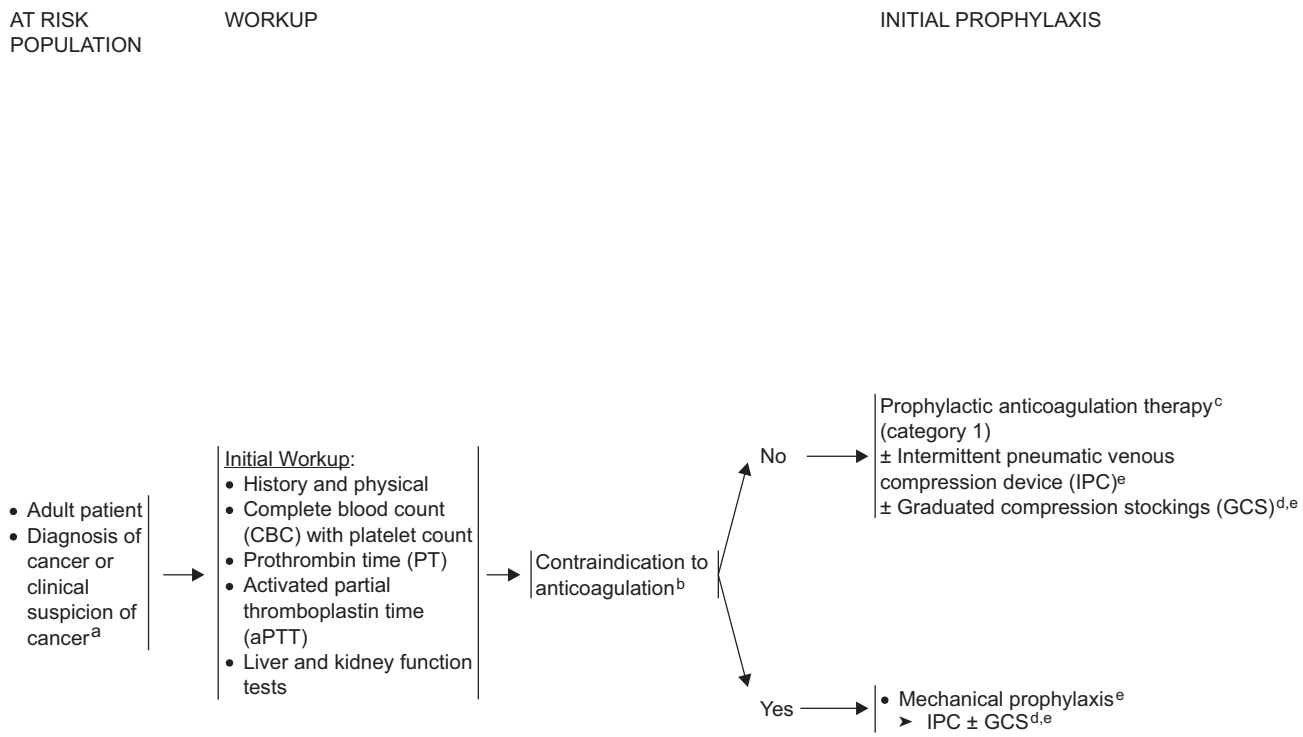
INPATIENT VENOUS THROMBOEMBOLISM PROPHYLAXIS



[a] See VTE Risk Factors in Cancer Patients (VTE-A).
[b] See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
[c] Pharmacologic intervention. See Inpatient/Outpatient Prophylactic Anticoagulation Treatment (VTE-C).
[d] Patient should be appropriately measured for stockings and monitored for adverse effects including skin ulcerations, especially in immobilized patients with peripheral neuropathy. See Contraindications to Mechanical Prophylaxis (VTE-B). (CLOTS Trial Collaboration. 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. See Contraindications to Mechanical Prophylaxis (VTE-B).

VTE-1

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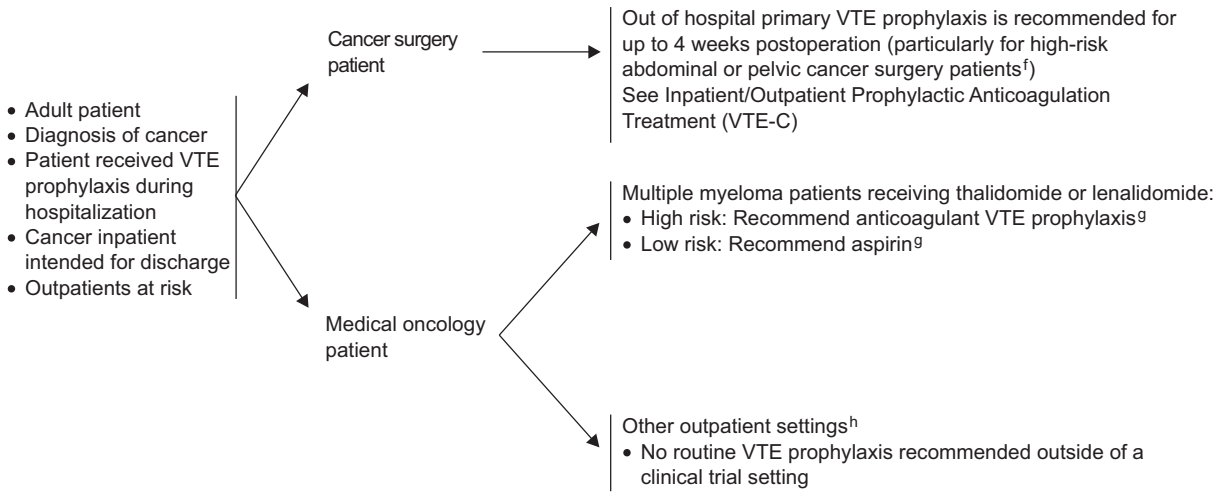
VTE PROPHYLAXIS FOLLOWING DISCHARGE AND FOR AMBULATORY CANCER PATIENTS AT RISK[a]

AT RISK POPULATION



[a] See VTE Risk Factors in Cancer Patients (VTE-A).
[f] High-risk abdominal/pelvic cancer surgery patients include those undergoing surgery for gastrointestinal malignancies, with a previous history of VTE, with anesthesia time >2 h, on bed rest >4 d, with advanced-stage disease, and age >60 y.
[g] Multiple myeloma patients receiving thalidomide/lenalidomide: in combination with high-dose dexamethasone (≥480 mg per month) or doxorubicin or multiagent chemotherapy or for myeloma patients with ≥2 individual or myeloma risk factors (See VTE Risk Factors in Cancer Patients [VTE-A 2 of 3]), recommended prophylaxis is LMWH (enoxaparin, 40 mg subcutaneous every 24 h or its equivalent) or warfarin (adjusted to INR 2-3). For low-risk myeloma patients with ≤1 individual or myeloma risk factors, aspirin, 81-325 mg daily may be used. Aspirin should not be used in nonmyeloma patients for VTE prevention.
[h] Consider a patient conversation regarding risks and benefits of VTE prophylaxis in the patient population with a Khorana score ≥3. (See Khorana Predictive Model for Chemotherapy-Associated VTE [VTE-A 3 of 3])

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 cancers
- Regional bulky lymphadenopathy with extrinsic vascular compression
- Familial and/or acquired hypercoagulability (including pregnancy)
- Medical comorbidities: infection, renal disease, pulmonary disease, congestive heart failure, arterial thromboembolism
- Poor performance status
- Older age

High-risk outpatients on chemotherapy, based on combinations of the following risk factors[1]
- Active cancers associated with high incidence of VTE: stomach, pancreas, lung, lymphoma, gynecologic, bladder, and testicular
- Prechemotherapy platelet count >300,000/mcL
- Prechemotherapy WBC >11,000/mcL
- Hemoglobin <10 g/dL
- Use of erythropoietic-stimulating agent s
- Body mass index ≥35 kg/m^2
- Prior VTE

Treatment-related risk factors
- Major surgery
- Central venous catheter/IV catheter
- Chemotherapy such as:
  - Thalidomide/lenalidomide plus high-dose dexamethasone
- Exogenous hormonal therapies such as:
  - Hormone replacement (HRT)
  - Contraceptives
  - Tamoxifen/raloxifene
  - Diethylstilbestrol

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

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

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VTE RISK FACTORS IN CANCER PATIENTS

Risk Assessment Model for the Management of Venous Thromboembolism in Multiple Myeloma Patients Treated With Thalidomide or Lenalidomide[1]

Risk factors	Recommended action
Individual risk factors • Obesity (BMI=30 kg/m^2) • Prior VTE • CVAD or pacemaker • Associated disease: ➤ Cardiac disease ➤ Chronic renal disease ➤ Diabetes ➤ Acute infection ➤ Immobilization • Surgery: ➤ General surgery ➤ Any anesthesia ➤ Trauma • Use of erythropoietin • Blood clotting disorders	No risk factor or only one individual/myeloma risk factor: • Aspirin, 81-325 mg once daily ≥2 individual/myeloma risk factors: • LMWH (equivalent to enoxaparin, 40 mg once daily; or • Full-dose warfarin (target INR 2-3)
Myeloma-related risk factors • Diagnosis of myeloma, per se • Hyperviscosity	
Myeloma therapy • Thalidomide or lenalidomide in combination with: ➤ High-dose dexamethasone (=480 mg per month) ➤ Doxorubicin ➤ Multiagent chemotherapy	Therapies as described in the left column: • LMWH (equivalent to enoxaparin, 40 mg once daily); or • Full-dose warfarin (target INR 2-3)

[1] Reproduced with permission from Macmillan Publishers Ltd: Leukemia. Palumbo A, Rajkumar SV, Dimopolous MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-423. Copyright 2008. http://www.nature.com/leu/journal/v22/n2/full/2405062a.html.

VTE RISK FACTORS IN CANCER PATIENTS

Khorana Predictive Model For Chemotherapy-Associated VTE[1]

Patient Characteristic	Risk Score
• Site of primary cancer	
➤ Very high risk (stomach, pancreas)	2
➤ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• Prechemotherapy platelet count ≥350 x 10^9/L	1
• Hemoglobin level <10 g/dL or use of red cell growth factors	1
• Prechemotherapy leukocyte count >11 x 10^9/L	1
• BMI ≥35 kg/m^2	1

Total Score	Risk Category	Risk of Symptomatic VTE[2]
0	Low	0.8%-3.0%
1, 2	Intermediate	1.8%-8.4%
≥3	High	7.1%-41.0%

[1] Reproduced and adapted with permission from Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-4907; and Tafur AJ, Kalsi H, Wysokinski WE, et al. The association of active cancer with venous thromboembolism location: a population-based study. Mayo Clin Proc 2011;86:25-30.

[2] Kearney JC, Rossi S, Glinert K, Henry DH. Venous thromboembolism (VTE) and survival in a cancer chemotherapy outpatient clinic: a retrospective chart review validation of a VTE predictive model [abstract]. Blood 2009;114:Abstract 2503; Price LH, Nguyen MB, Picozzi VJ, Kozarek RA. Portal vein thrombosis in pancreatic cancer: natural history, risk factors, and implications for patient management [abstract]. Presented at the 2010 Gastrointestinal Cancers Symposium; January 22–24, 2010; Orlando, Florida. Abstract 143; and Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. Blood 2010;116:5377-5382.

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CONTRAINDICATIONS TO PROPHYLACTIC OR THERAPEUTIC ANTICOAGULATION TREATMENT

Absolute
- Recent central nervous system bleed, intracranial or spinal lesion at high risk for bleeding
- Active bleeding (major): >2 units transfused in 24 h
- Spinal anesthesia/lumbar puncture[1]

Relative
- Chronic, clinically significant measurable bleeding >48 h
- Thrombocytopenia (platelets <50,000/mcL)
- Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)
- Recent major operation at high risk for bleeding
- Underlying hemorrhagic coagulopathy
- High risk for falls (head trauma)

CONTRAINDICATIONS TO MECHANICAL PROPHYLAXIS

Absolute
- Acute DVT
- Severe arterial insufficiency (pertains to GCS only)

Relative
- Large hematoma
- Skin ulcerations or wounds[2]
- Thrombocytopenia (platelets <20,000/mcL) or petechiae
- Mild arterial insufficiency (pertains to GCS only)
- Peripheral neuropathy (pertains to GCS only)

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

[2] Skin ulcerations and wounds are more problematic with the use of GCS.

VTE-B

INPATIENT/OUTPATIENT PROPHYLACTIC ANTICOAGULATION TREATMENT[1-3]

- LMWH[4]: (category 1 for inpatient)
  - Dalteparin, 5000 units subcutaneously daily
  - Enoxaparin, 40 mg subcutaneously daily
  - Tinzaparin,[5] 4500 units (fixed dose) subcutaneously daily or 75 units/kg subcutaneously daily
- Fondaparinux[6] (category 1 for inpatient)
  - Fondaparinux, 2.5 mg subcutaneously daily
- Unfractionated heparin: 5000 units subcutaneously every 8-12 h (category 1 for inpatient)
- Aspirin, 81-325 mg daily (for low-risk multiple myeloma outpatients only)[7]
- Warfarin (adjusted to INR 2-3)[8]

For diagnosis and treatment of heparin-induced thrombocytopenia (HIT), see HIT-1, in these guidelines, available online, at NCCN.org.

[1] Agent selection based on:
- Renal failure (creatinine clearance <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. (Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e195S-226S; and Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e24S-43S).

[3] Following initiation of heparin: hemoglobin, hematocrit, and platelet count every 2-3 d up to at least day 14 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-Xa monitoring may be required. Follow package insert for renal dysfunction and body weight-based dosing.

[5] Tinzaparin should be avoided in patients aged >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 creatinine clearance <30 mL/min. It should be used with caution in patients with moderate renal insufficiency (creatinine clearance, 30-50 mL/min), weight <50 kg or age >75 y.

[7] Use only for lower-risk multiple myeloma outpatients with ≤1 individual or myeloma risk factors (See VTE Risk Factors in Cancer Patients [VTE-A]).

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

VTE-C

Text cont. from page 1403.

direct vascular compression.[6–8] The incidence of cancer-associated VTE is further increased by the presence of additional risk factors, such as acquired or congenital thrombophilia (eg, antiphospholipid syndrome, factor V Leiden), prolonged immobilization, surgical procedures, and chemotherapeutic regimens.[7,9] The occurrence of VTE has been reported to increase the likelihood of death for patients with cancer by 2- to 6-fold.[10–14] For example, patients with gynecologic cancer with PE were found to have a 6-fold increased risk of death at 2 years compared with similar patients without PE.[13] Furthermore, VTE has been reported to be the most common cause of death at 30-day follow-up among patients with cancer undergoing surgery.[15]

The NCCN Guidelines for VTE are reviewed and updated annually by a multidisciplinary panel of experts (including medical and surgical oncologists, hematologists, cardiologists, internists, and pharmacists) to provide recommendations on the diagnosis, prevention, and treatment of VTE in patients with cancer. The following sections of the NCCN Guidelines focus on risk factors for VTE in patients with cancer, identification of patients at risk for VTE, and strategies for thromboprophylaxis in at-risk patients with cancer. The full version of these guidelines, available on the NCCN Web site at_NCCN.org, also includes sections on the evaluation and treatment of VTE by site (eg, lower extremity DVT, SVT, splenic portal vein thrombosis, CVAD-related DVT, PE), an overview of anticoagulants used in the treatment of VTE, a discussion of the management of heparin-induced thrombocytopenia (HIT), and recommendations for reversal of anticoagulation.

VTE Risk Assessment in Patients with Cancer

Many of the risk factors for development of VTE are common to patients with cancer.[16,17] VTE risk factors in these patients can be grouped into 3 general categories: patient-related factors (ie, intrinsic and extrinsic), cancer-related factors, and treatment-related factors (see VTE-A 1 of 3, page 1406). VTE risk factors in individual patients are likely to be represented by all 3 risk factor categories, and the VTE risk conferred by a single risk factor cannot be evaluated in isolation.

More advanced age, a common characteristic of many patients with cancer, was shown to be associated with an increased risk of VTE in some clinical settings.[1,15,18,19] In addition, obesity has been identified as a risk factor for VTE.[18,20–22] Evidence also suggests that prechemotherapy thrombocytosis,[22–24] leukocytosis,[22] and a hemoglobin level less than 10 g/dL[22,23] are predictive of VTE in patients undergoing chemotherapy, although the association of anemia with VTE may be complicated by the use of erythropoiesis-stimulating agents (ESAs). Acquired risk factors for VTE include a history of VTE and certain hypercoagulable conditions, such as pregnancy. A history of prior VTE has been identified in several studies as an independent risk factor for developing a subsequent VTE.[15,21,24–27] Moreover, recurrent VTE was found to be more common among patients with cancer; for example, 12-month cumulative incidences of recurrent VTE of 20.7% and 6.8% were reported for patients with and without cancer, respectively, undergoing anticoagulant treatment.[28] Although factor V Leiden and prothrombin mutations were identified in 3.7% and 2.6%, respectively, of patients with breast or colon cancer receiving adjuvant chemotherapy in a recent prospective observational study, these inherited risk factors were not associated with an increased risk of VTE among patients with cancer.[24]

Several other patient-related VTE risk factors, although not exclusive to patients with cancer, are commonly found, including hospitalization, other medical comorbidities (eg, infection), poor performance status, and prolonged immobilization.[4] In the latest report from the Centers for Disease Control and Prevention,[19] VTE events were found to occur at a high rate among hospitalized patients. Among hospitalized adults, VTE was reported in more than 547,000 patients annually (annual rate of 239 per 100,000 persons hospitalized) with more than 28,700 deaths annually in these patients.[19] The risk for VTE increased with age in hospitalized patients. This report confirms that hospitalization is an important risk factor for VTE, and emphasizes the need for greater awareness of VTE risks and appropriate implementation of preventive measures in this setting. Infection has also been identified as an important risk factor for VTE, including in patients with cancer.[29,30] A recently published case-crossover study in individuals (≥51 years of age) hospitalized for VTE (n=399 among N=16,781 participating in the Health and

Retirement Study) reported that infections, use of ESAs, blood transfusions, major surgeries, fractures, immobility, and chemotherapy were significant risk factors for VTE hospitalization.[29] In the subgroup of patients with cancer from this study, the major predictors of VTE hospitalization were infections, blood transfusions, and insertion of a central venous catheter.[29] In a recent population-based case-control study in patients with hospital-diagnosed VTE (N=15,009), the estimated incidence rate for VTE was increased by 3-fold among patients within the first 3 months after infection compared with those without an infectious event during the year before VTE (incidence rate ratio, 3.3 after adjustment for other VTE risk factors).[30]

Several VTE risk factors are exclusive to patients with cancer, including the presence of malignancy, exposure to chemotherapy, and extrinsic vascular compression from cancer-associated regional bulky lymphadenopathy. Results from 2 population-based case-control studies showed that the presence of cancer increased the risk of VTE 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.[25,33] Furthermore, researchers have reported cancer as the cause of approximately 20% of the VTE cases seen in the community,[4] and a recent cancer diagnosis and the occurrence of advanced malignancies and distant metastases also increase VTE risk.[2,21,31,34,35] For example, Blom et al[31] reported an adjusted odds ratio of 19.8 for VTE risk in patients with solid tumor cancers with distant metastases compared with patients without. In addition, tumor histology has been shown to influence the risk of VTE in patients. Several studies have evaluated the association between different types of cancer and the risk of developing VTE.[1–3,10,31,33,36] For example, pancreatic cancer[1–3,10,33,34,36] and brain tumors[1,2,31,37–39] were associated with a high risk of VTE in several of the 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.[1,3,18,31,40] In addition, an increased risk of VTE has been observed in certain hematologic malignancies, such as lymphoma, acute leukemia, and multiple myeloma.[1,41,42] Patients with high-grade lymphoma and acute promyelocytic leukemia seem to be at higher risk than those with other forms of lymphoma or leukemia.[41] 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.[43]

Several factors associated with an increased risk of VTE 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).[42] Further validation of the influence of these risk factors on VTE rates in patients with myeloma is warranted. In contrast, breast cancer was associated with a relatively low VTE risk in some studies.[1,11,44] Nevertheless, because of the relatively high prevalence of breast cancer, the occurrence of VTE in a patient 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.[11]

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 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 patients with cancer has been shown in several studies.[22,23,45] For example, in one population-based case-control study, odds ratios of 6.5 and 4.1 for the development of VTE were determined when patients receiving chemotherapy and those not receiving chemotherapy, respectively, were

compared with patients without a malignant neoplasm.[32] In another retrospective study, the annual incidence of VTE was 15% in patients with colorectal cancer treated with chemotherapeutic regimens.[9] Khorana et al[22] published a risk assessment model to estimate the risk of VTE in ambulatory patients with cancer receiving chemotherapy. This risk assessment model has been recently validated and extended by Ay et al,[46] who identified D-dimer and P-selectin as additional discriminatory risk factors for VTE in ambulatory patients with cancer. However, these laboratory tests are not routinely measured in patients with cancer, 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,[22] 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 patients with cancer undergoing chemotherapy.

Increased VTE risk was shown to be associated with the use of exogenous hormonal compounds, such as selective estrogen receptor modulators (eg, tamoxifen, raloxifene), for the prevention and treatment of certain estrogen receptor–positive cancers.[47–51] The use of hormonal compounds such as hormone replacement therapy[52,53] or oral contraceptive agents[54–57] has also been associated with increased risk of developing VTE. Recent case-control studies and meta-analyses suggested that, for combined oral contraceptives, VTE risks may differ between formulations, depending on the type of progestogen used.[56,58,59] 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.[60] Evidence has supported the association of immunomodulating agents that have antiangiogenic properties (eg, 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.[42,61–66] Other agents used in supportive cancer care (eg, ESAs) have also been associated with the development of VTE.[3,23,40,67] The concomitant use of erythropoietin and other therapies associated with the development of VTE (eg, lenalidomide) may further increase VTE risk.[64]

Results from numerous studies have identified the presence of a CVAD as a risk factor for the development of an upper-extremity DVT,[32,68–70] although discrepancies exist concerning the incidence of CVAD-related DVT.[70,71] 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[70,72,73] or infections occurring as a result of catheter placement.[73,74] 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 diagnostic strategies used in some of the studies (ie, clinical, which identifies symptomatic events, vs radiologic surveillance, which identifies symptomatic and asymptomatic events).[70,71]

Therapies for Prophylaxis or Treatment of VTE in Patients With Cancer

Anticoagulants

Anticoagulation agents used in the prophylaxis and/or treatment of VTE are listed and described according to guideline recommendations (see VTE-C, page 1410). FDA indications and NCCN recommendations for use of each of these therapies are listed in the NCCN Drugs & Biologics Compendium (NCCN Compendium) for Venous Thromboembolic Disease (for the latest version of the NCCN Compendium, please visit NCCN.org). The panel recommends that agent selection be based on criteria such as the presence of renal insufficiency, FDA approval, cost, ease of administration, need for therapeutic monitoring, and ease of reversibility. Suggested dosing schedules included within this guideline (see VTE-C, page 1410) were established according to the 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 documents. Recommendations of the American College of Chest Physicians provide another legitimate source for anticoagulant dosing schedules.[75–77]

Low-Molecular-Weight Heparins: 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 the 3 LMWHs are commonly considered therapeutically equivalent and are often used interchangeably, few clinical studies have tested whether the clinical effects of these agents are comparable. Furthermore, the 3 agents differ pharmacologically with respect to mean molecular weight, half-life, and ability to inhibit thrombin and factor Xa. Results from a randomized clinical study comparing tinzaparin and 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,[78] 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[79] is approved by the FDA for both prophylaxis and immediate treatment of VTE; tinzaparin[80] is currently approved only for immediate VTE treatment; and dalteparin[81] 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.[78,82–86] Extended or chronic anticoagulation therapy with an LMWH may require dosage reduction after an initial period. For example, in the CLOT study, the dalteparin dose was reduced from 200 IU/kg every day to 150 IU/kg every day after 1 month.[83] In addition, the ESMO clinical recommendations for management of VTE in patients with cancer specify using 75% to 80% of the initial dose of LMWH for extended anticoagulation therapy.[87] 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 (age ≥70 years), and patients with cancer.[88–90] Of the 3 LMWHs, specific dosing recommendations for patients with severe renal insufficiency (creatinine clearance [C_{Cr}] <30 mL/min) are available only for enoxaparin.[79,91] Manufacturer recommendations specify 30 mg of subcutaneous enoxaparin daily for VTE prophylaxis and 1 mg/kg subcutaneously every 24 hours for VTE treatment for patients with C_{Cr} less than 30 mL/min. These recommendations are supported by the results of a meta-analysis showing enoxaparin to be associated with a 2- to 3-fold increased risk of bleeding when administered in standard, unadjusted therapeutic doses to patients with severe renal insufficiency compared with those without severe renal insufficiency.[92] In another study, renal clearance of enoxaparin was shown to be reduced by 31% and 44% in patients with moderate (30–60 mL/min) and severe renal impairment (<30 mL/min), respectively, leading the authors to suggest dose reductions for patients with C_{Cr} values less than 50 mL/min.[93] Furthermore, some evidence supports downward dose adjustments of enoxaparin in the management of patients with C_{Cr} of 30 to 60 mL/min.[94]

Some data are available with respect to the safety of dalteparin and tinzaparin in patients with renal insufficiency. In a small study of patients (N=22) treated with dalteparin, mean anti-Xa activity was similar between patients with renal impairment (mean $C_{Cr,}$ 26 mL/min; range, 16–38 mL/min) and those with normal renal function (C_{Cr} >80 mL/min).[95] In a more recent study of prophylactic dalteparin in critically ill patients (N=138 evaluable) with severe renal impairment (C_{Cr} <30 mL/min), no bioaccumulation was detected after a median of 7 days of prophylactic-dose dalteparin (5000 IU daily).[96] Treatment was not associated with excessive anticoagulation; peak anti-Xa levels were between 0.29 and 0.34 IU/mL.[96] For patients with cancer with C_{Cr} less than 30 mL/min receiving dalteparin for extended treatment of acute VTE, the manufacturer recommends monitoring of peak anti-Xa levels to achieve a target range of 0.5 to 1.5 IU/mL. LMWH anti-Xa levels should be measured 4 to 6 hours after dosing, and only after the patient has received 3 to 4 doses of dalteparin.[81] 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,[97] or in elderly patients (age >70 years) with renal insufficiency (but C_{cr} >20 mL/min) receiving therapeutic doses of tinzaparin (175 IU/kg daily) for 10 days.[98,99] However, results from a randomized clinical trial of elderly patients with a C_{Cr} level less than 60 mL/min undergoing initial treatment for VTE showed a substantially higher mortality rate in the arm receiving tinzaparin than in the group receiving unfractionated heparin (UFH; 11.2% vs 6.3%; *P*=.049).[100] 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 and older with renal insufficiency.

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.[79] The panel also recognizes current evidence suggesting caution 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 those with cancer.

Concerns also exist about maintaining and monitoring therapeutic concentrations of anticoagulants in obese patients. In one study, thromboprophylaxis with 5000 IU per day of dalteparin 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.[101] Hospitalization of morbidly obese patients with cancer during 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,[79–81] the panel also recommends caution when using these agents in patients with low body weight and in elderly patients. LMWHs are contraindicated in patients with HIT, and should only be used with caution in patients with a history of HIT. In this situation, a direct thrombin inhibitor (DTI) or fondaparinux represent safer alternatives.

Factor Xa Inhibitors: Fondaparinux is a parenteral indirect factor Xa inhibitor approved by the FDA for the prophylaxis of DVT in patients undergoing hip fracture surgery, hip or knee replacement surgery, or abdominal surgery, and for the treatment of VTE (DVT or acute PE) when administered in conjunction with warfarin.[102] 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.[102–105] However, the use of fondaparinux in patient populations with renal insufficiency, obesity, or HIT has not been well defined,[90,105] although some evidence supports its safe and effective use for VTE prophylaxis in older patients with a broad range of body weights.[106] Pharmacologic characteristics of fondaparinux include renal elimination and a very long half-life of 17 to 21 hours.[102] Prescribing information for fondaparinux provided by the manufacturer specifies that the drug is contraindicated in patients with severe renal insufficiency (C_{cr} <30 mL/min) and for thromboprophylaxis in patients weighing less than 50 kg undergoing orthopedic or abdominal surgery.[102] It should be used with caution in elderly patients[106] and individuals with moderate renal insufficiency (C_{cr} <50 mL/min).[102] 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, those with renal dysfunction ($C_{cr,}$ 30–50 mL/min), and elderly patients (>75 years of age).

Rivaroxaban is an orally administered direct factor Xa inhibitor approved by the FDA for the prevention of VTE in patients undergoing hip or knee replacement surgery and for the initial and long-term treatment of DVT/PE and prevention of thromboembolism in patients with nonvalvular atrial fibrillation.[107] The drug is primarily eliminated via the kidneys (66% renal excretion), with a lesser proportion cleared by hepatic metabolism (cytochrome P450 3A4–dependent and –independent mechanisms). Rivaroxaban is considered a low-clearance drug, because protein binding in plasma is high (92%–95%).[107] The half-life is 5 to 9 hours in healthy individuals (age 20–45 years) and extends to 11 to 13 hours in older patients. The prescribing information for rivaroxaban provided by the manufacturer specifies that the drug should be avoided in patients with severe renal impairment (C_{cr} <30 mL/min) and should be used with caution in those with moderate impairment (C_{cr}, 30–50 mL/min).[107] Randomized clinical trials have compared rivaroxaban with the LMWH enoxaparin for thromboprophylaxis in hospitalized acutely ill medical patients[108] and for chronic anticoagulation therapy to prevent recurrent VTE in patients who experienced an initial VTE event (PE with or without DVT).[109] Although results showed noninferiority of rivaroxaban compared with enoxaparin, the proportion of enrolled patients with active cancer was very low (5%–6%) in these studies. Until further data become available in patients with cancer, the panel does not recommend using this agent for prophylactic or therapeutic anticoagulation in patients with cancer.

Apixaban is another orally administered direct factor Xa inhibitor recently approved by the FDA for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation.[110] Apixaban is primarily metabolized via the liver (cytochrome P450 3A4–dependent); renal elimination accounts for approximately 27% of total drug clearance. The apparent half-life after oral administration of the drug is approximately 12 hours.[110] The prescribing information for apixaban provided by the manufacturer specifies that the drug should be avoided in patients with severe renal impairment (C_{cr} <15 mL/min; patients with a C_{cr} <25 mL/min were excluded from clinical trials with apixaban) or hepatic impairment (patients with transaminases >2 times the upper limit of normal or total bilirubin >1.5 times the upper limit of normal were excluded from clinical trials with apixaban). Recent randomized clinical trials have evaluated the potential role of apixaban for thromboprophylaxis in hospitalized acutely ill medical patients (compared with the LMWH enoxaparin)[111] and for initial and extended anticoagulation therapy in patients who completed initial anticoagulation for VTE (compared with placebo).[112] Apixaban (2.5 mg twice daily for 30 days) was not superior to a standard course of enoxaparin (40 mg once daily for 6–14 days) in preventing VTE in acutely ill patients and was associated with an increased risk for major bleeding events.[111] In a randomized double-blind study of apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) versus conventional therapy (enoxaparin, 1 mg/kg subcutaneously every 12 hours followed by warfarin to a target international normalized ratio [INR] of 2–3) for the treatment of patients with acute VTE (AMPLIFY trial), apixaban was noninferior to enoxaparin/warfarin in preventing recurrent VTE or VTE-related death (2.3% vs 2.7%; relative risk, 0.84; 95% CI, 0.60–1.18).[113] The incidence of major bleeding was 0.6% in the apixaban arm and 1.8% in the enoxaparin/warfarin arm (relative risk, 0.31; 95% CI, 0.17–0.55; *P*<.001 for superiority) Only 143 patients with cancer (2.7%) were enrolled in this trial.[113] In a randomized study involving patients who received 6 to 12 months of anticoagulation for chronic VTE management, extended treatment with apixaban was associated with a significantly decreased risk of recurrent VTE compared with placebo.[112] However, only a small percentage of patients with active cancer (1.7%) were included in this study. As in the case with rivaroxaban mentioned earlier, the panel currently does not recommend apixaban for thromboprophylaxis or for the treatment of VTE because of the lack of sufficient clinical data in patients with cancer.

Unfractionated Heparin: UFH is generally administered subcutaneously for VTE prophylaxis (low-dose heparin) and through intravenous infusion for the treatment of VTE.[114] Low-dose UFH (5000 IU) administered 3 times per day (every 8 hours) was shown to be more effective than low-dose UFH administered twice daily in preventing DVT in general surgery patients[115] and is the regimen recommended by the panel for VTE prophylaxis in patients with cancer. However, no difference in the overall rate of VTE based on the dosing of prophylactic UFH (5000 IU twice daily versus 3 times daily) was observed in a meta-analysis of clinical trials conducted in general medical patients, although a decrease was seen in the combined end point of proximal DVT and PE (*P*=.05) and the risk of major bleeding was significantly higher when UFH was administered 3 times daily (*P*<.001).[116,117]

Initial dosing of UFH in the treatment of VTE is weight based, with a recommended regimen of 80 U/kg bolus followed by 18 U/kg per hour infusion.[89] The safety and efficacy of fixed dose, unmonitored, subcutaneous UFH has been reported to be comparable to LMWH in the treatment of patients with acute VTE,[118] but further investigation is warranted before this regimen can be routinely used in patients with cancer. Patients receiving intravenous UFH must be hospitalized and monitored for anticoagulant response. The panel recommends UFH as the agent of choice in patients with C_{cr} less than 30 mL/min, because the liver is a main site of heparin biotransformation.[103,119] 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.

Warfarin: Warfarin is an option for the long-term treatment of VTE in patients with cancer. If warfarin is to be used for chronic therapy, it should be administered concomitantly with UFH, LMWH, or fondaparinux for at least 5 days and until an INR of

2 or more is achieved before discontinuing the parenteral anticoagulant agent. When treating patients with HIT, warfarin should not be initiated until the platelet count has recovered, and then it should be overlapped with a DTI or fondaparinux for at least 5 days and until the INR is 2 or more. During the transition to warfarin monotherapy, the INR should be measured at least twice weekly, and then initially at least weekly once the patient is receiving warfarin monotherapy. Warfarin can be safely administered to patients with renal insufficiency, although the response to warfarin is accentuated in patients with hepatic insufficiency.[120]

Direct Thrombin Inhibitors: DTIs are discussed under Diagnosis and Treatment of HIT in the full version of the NCCN Guidelines for VTE (available at NCCN.org).

Aspirin

Aspirin (81–325 mg/d) is an option for VTE prophylaxis in only a select group of patients with multiple myeloma at low risk for VTE (≤1 individual or multiple myeloma risk factors; see VTE-2, page 1405). Aspirin is not considered to be effective VTE prophylaxis in other settings. In the Women's Health study, a 10-year study of healthy women randomly assigned to aspirin (100 mg) or placebo on alternate days, no significant differences in the incidence of VTE were observed between the arms.[121] Thus, aspirin provided no benefit for initially healthy women who had no or very few risk factors for VTE. A recent double-blind, randomized, controlled study compared the efficacy and safety of aspirin (100 mg daily; n=205) versus placebo (n=197) in patients with a first unprovoked VTE who had completed 6 to 12 months of oral anticoagulation therapy before study initiation.[122,123] Study treatment was administered for at least 2 years. During the study period (median, 24.6 months), VTE recurrence occurred in 14% and 22% of patients who received aspirin and placebo, respectively; this translated to a significant reduction in risk of VTE recurrence with aspirin (6.6% vs 11.2% per year; hazard ratio, 0.58; 95% CI, 0.36–0.93).[123] The incidence of clinically relevant bleeding events was similar between study arms; major bleeding occurred in 1 patient in each arm. Notably, a second study of adults with unprovoked VTE (N=822; the ASPIRE trial) did not identify significant benefit with low-dose aspirin (100 mg daily) compared with placebo in preventing recurrent VTE (4.8% vs 6.5% per year; hazard ratio, 0.74; 95% CI, 0.52–1.05; *P*=.09).[124] Given the conflicting results of aspirin therapy for preventing VTE and the exclusion of patients with cancer from these studies, aspirin cannot be recommend for extended treatment of VTE in these patients.

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 until patients are fully ambulatory. Graduated compression stockings (GCS) can be used in conjunction with an IPC device as a method of mechanical prophylaxis. However, GCS were ineffective for VTE prevention in patients with acute stroke and were associated with a 4-fold increased risk of skin ulcerations.[125] Therefore, GCS should not be used for VTE prophylaxis in patients with cancer.

Vena Cava Filters: Vena cava filters are indicated for the prevention of PE in patients who cannot be anticoagulated because of an absolute contraindication to therapeutic anticoagulation or complications from anticoagulation.[126–130] However, placement of an IVC filter does not prevent DVT and has been associated with an increased risk of recurrent DVT.[126,131,132] A randomized, controlled trial has assessed the efficacy and safety of IVC filters in conjunction with anticoagulation compared with anticoagulant therapy alone in the treatment of acute VTE. However, this pivotal trial did not test the efficacy of IVC filters in the usual clinical scenario: in patients without concomitant anticoagulation.[126,131] Whether IVC filter placement is beneficial in the absence of iliopopliteal lower-extremity, IVC, or pelvic DVT is unclear.

Both retrievable ("optional") and permanent IVC filters are available; however, the recovery period for a retrievable filter is limited.[133,134] Results from a retrospective cohort study of 702 patients with IVC filter placement showed that filter retrieval was attempted for only 15.5% of patients who received a retrievable filter, and only approximately 70% of those attempts were successful.[135] No significant differences in PE protection or complication rates were observed between the 2 filter types, although mean follow-up time was limited to 11.5 months. A

recent case series of patients who received 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.[136] Whether the frequency of this complication is device-specific or a characteristic 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.

Anticoagulation in Patients With Cancer

Contraindications to Anticoagulation

Contraindications to anticoagulation can be relative (ie, anticoagulation is not prohibited in all clinical situations) or absolute (ie, anticoagulation is prohibited in all clinical situations) and temporary or permanent. Consideration of the degree of contraindication to anticoagulation and the duration of anticoagulation (temporary or permanent) is essential when evaluating its risks and benefits in the individual patient. Absolute contraindications to anticoagulation include recent central nervous system bleeding or intracranial or spinal lesions at high risk for bleeding, major active bleeding (requiring >2 units of blood transfusions in 24 hours), or recent spinal anesthesia/lumbar puncture (see VTE-B, page 1409). Relative contraindications, for which the risks and benefits of anticoagulation must be considered on an individual basis, include chronic, clinically significantly bleeding (for >48 hours), recent major surgery associated with a high risk of bleeding, high risk for falls and/or head trauma, thrombocytopenia (platelets <50,000/mcL) or severe platelet dysfunction (eg, from uremia, medications, dysplastic hematopoiesis), or underlying hemorrhagic coagulopathy (see VTE-B, page 1409). The panel recommends frequent reevaluation of these contraindications and the risks and benefits of anticoagulation therapy for any patient with cancer considered to be at increased risk for bleeding.

Patients with a recent history of bleeding associated with the central nervous system or a spinal lesion are at increased risk of anticoagulant-associated bleeding. Package inserts for all 3 of the LMWHs and fondaparinux include boxed warnings specifying that the risk 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.[79–81,102] UFH should also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture.[119] Other factors, such as a patient's risk of falling, should also be considered before anticoagulation therapy is ordered.

A prolonged activated partial thromboplastin time (aPTT) is not considered a contraindication to anticoagulation therapy in patients with a lupus inhibitor or lupus anticoagulant (eg, antiphospholipid syndrome). Antiphospholipid antibodies prolong the aPTT through interfering with the interaction of 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 venous and arterial thromboembolism and adverse pregnancy outcomes.[137–139] Any patient who has experienced a thrombotic event and fulfills diagnostic criteria for antiphospholipid syndrome should be considered for indefinite anticoagulation therapy.[138]

VTE Prophylaxis

Prophylactic Anticoagulation Therapy

Inpatient Prophylactic Therapy: Hospitalized patients with cancer are at a high risk of developing VTE.[1,140] 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 this therapy (category 1; see VTE-1, page 1404). This recommendation is based on an assumption that ambulation in hospitalized patients with cancer is inadequate to reduce VTE risk. Recommended anticoagulant options for VTE prophylaxis of inpatients with cancer are listed in the guidelines (see VTE-C, page 1410). The LMWHs, fondaparinux, and subcutaneous UFH (5000 IU 3 times daily) are category 1 options for inpatient prophylactic therapy. Anticoagulation therapy should be administered throughout the duration of hospitalization. Adult patients with cancer should undergo the following evaluation before the initiation of thromboprophylaxis: comprehensive medical history and physical examination; CBC with platelet count and differential; prothrombin time; aPTT; and liver and kidney function tests (see VTE-1, page 1404).

Studies comparing different anticoagulant regimens for preventing VTE in patients with cancer have not clearly identified a particular regimen with superior efficacy. In a randomized multicenter clinical trial, no differences in VTE and bleeding rates were seen in 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.[141] 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.[142] However, results from a nonrandomized, historically controlled study comparing the effectiveness of the LMWH dalteparin (5000 IU once daily) versus low-dose UFH (5000 IU 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.[143] More recently, a meta-analysis comparing outcomes of perioperative VTE prophylaxis with LMWH versus UFH in patients with cancer showed no differences in rates of mortality, suspected DVT, PE, or bleeding events.[144]

For prevention of CVAD-associated VTE, randomized controlled studies have not established the efficacy of prophylactic doses of LMWH or low-dose warfarin (1 mg daily).[145–147] A recent randomized trial showed that dose-adjusted warfarin (INR, 1.5–2.0; n=473) was significantly more effective than fixed-dose warfarin (1 mg daily; n=471) in preventing CVAD-associated VTE at a cost of a trend toward more bleeding; however, a separate comparison of warfarin (fixed 1-mg dose, n=324; adjusted-dose, INR1.5–2, n=84) with placebo (n=404) did not demonstrate a statistically significant reduction in VTE.[148] These data suggest therapeutic or near-therapeutic doses of anticoagulation will likely be necessary for the successful prevention of CVAD-associated VTE. Until additional data are available, the panel does not recommend VTE prophylaxis in patients with cancer who have a CVAD.

Outpatient Prophylactic Therapy in Ambulatory Patients With Cancer: Certain groups of patients with cancer are known to remain at risk for VTE after discharge from the hospital. In a retrospective observational study based on data from a large cohort of patients with cancer (N=17,874) identified in a health care claims database, VTE (DVT or PE) occurred in nearly 6% of patients during the 12-month index period.[149] A significantly higher proportion of VTE events was diagnosed in the outpatient setting compared with the inpatient setting (78% vs 22%; $P<.0001$). Moreover, among patients who had a VTE in the outpatient setting, 21% had been hospitalized within 30 days of the VTE event.[149] This observational study suggests that a high proportion of VTE occurs in the cancer outpatient setting and underscores the need to better identify patients who may benefit from outpatient thromboprophylaxis. The risk of VTE is sufficiently high in some surgical and medical oncology patients that VTE prophylaxis should be considered in the outpatient setting (see VTE-2, page 1405, and VTE-C, page 1410). Cancer patients undergoing abdominal or pelvic surgery should be considered for outpatient prophylaxis.[150] Features that identify surgical oncology patients at higher risk for VTE include a previous episode of VTE, anesthesia times longer than 2 hours, advanced-stage disease, perioperative bed rest of 4 or more days, and patient age of 60 years or older.[15] Extended prophylaxis out to 4 weeks postsurgery was associated with a greater than 50% reduction in venographic VTE in patients undergoing major abdominal surgery.[151,152] Because thromboembolic postoperative complications greatly exceeded hemorrhagic complications as a cause of death in the @RISTOS observational cohort study of patients who underwent cancer surgery,[15] extended (up to 4 weeks) VTE prophylaxis is recommended for patients undergoing cancer surgery, particularly the high-risk patients undergoing abdominal or pelvic surgery.

Although extended outpatient prophylaxis lacks consistent evidence to support its use in most populations of ambulatory medical oncology patients,[153] it is recommended for patients with multiple myeloma receiving highly thrombogenic regimens. Immunomodulating agents with antiangiogenic properties, such as thalidomide or lenalidomide, have been associated with an increased incidence of VTE in patients with multiple myeloma in the absence of prophylaxis, although the reported rates of VTE vary widely across studies.[42,61,62,65,153,154] Several factors seems to contribute to thrombosis associated with thalidomide or its derivatives,[154] and VTE rates are especially high when thalidomide or lenalidomide is combined with high-dose dexamethasone (≥480 mg per month), or doxorubicin or multiagent chemotherapy regimens.[42,61,64–66] In a retrospective

case control study of thalidomide or lenalidomide combined with dexamethasone in patients with newly diagnosed multiple myeloma (N=411), the incidence of VTE among the subgroup of patients who received the combination with high-dose dexamethasone (480 mg per 28-day cycle) was 19% with thalidomide and 11% with lenalidomide.[155] Data regarding the use of routine thromboprophylaxis were not provided. In an open-label, randomized, noninferiority trial comparing lenalidomide combined with high-dose dexamethasone (480 mg per 28-day cycle) versus with low-dose dexamethasone (160 mg per 28-day cycle) in previously untreated patients with multiple myeloma (N=445), the incidence of DVT was significantly higher among the patients receiving the combination with high-dose dexamethasone (26% vs 12%; *P*=.0003).[156] Mandatory thromboprophylaxis was added to the study protocol after enrollment of approximately 60% of the patients. The package inserts for thalidomide and lenalidomide include black box warnings regarding the VTE risks associated with the administration of these agents.[157,158]

For patients with multiple myeloma, the panel recommends a prophylaxis strategy based on a risk assessment model published by The International Myeloma Working Group.[42] This model recommends VTE prophylaxis with either LMWH (eg, enoxaparin, 40 mg/d) or dose-adjusted warfarin (INR 2–3) for patients with multiple myeloma who are receiving lenalidomide- or thalidomide-based combination regimens associated with a high thrombotic risk, or for patients with 2 or more individual or disease-related risk factors (see VTE-A 2 of 3, page 1407). Aspirin prophylaxis (81–325 mg daily) is an option for patients with multiple myeloma receiving thalidomide or lenalidomide who have one or fewer individual or multiple myeloma risk factors.[42]

In a recent phase III open-label multicenter randomized trial in patients with previously untreated multiple myeloma (N=667) receiving thalidomide-containing regimens, both aspirin (100 mg daily) and fixed-dose warfarin (1.25 mg daily; dose adjustment allowed to maintain INR<3) were similarly effective in reducing thromboembolic events compared with LMWH (enoxaparin, 40 mg daily).[159] 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 5.0% in the aspirin, warfarin, and LMWH groups, respectively.[159] 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 grade 3/4 thromboembolic events and major bleeding events when compared with aspirin. However, LMWH was associated with a significantly decreased risk for grade 3/4 thromboembolic events when compared with warfarin (absolute difference, +5% for warfarin vs LMWH; *P*=.024). Moreover, among the subgroup of patients aged 65 years or older receiving combination therapy with bortezomib, melphalan, prednisone, and thalidomide, LMWH significantly reduced the risk for the composite end point compared with warfarin (absolute difference, +11.3 for warfarin vs LMWH; *P*=.006).[159] Notably, this study was conducted in patients with myeloma and at standard risk for thromboembolism, who had no clinical indication for anticoagulation or antiplatelet therapy.

As part of a substudy of a phase III open-label randomized trial, thromboprophylaxis with aspirin (100 mg daily) was compared with LMWH (enoxaparin, 40 mg daily) in patients with multiple myeloma (N=342) receiving lenalidomide-containing induction (combined with low-dose dexamethasone) and consolidation (combined with melphalan and prednisone).[160] The primary end point was a composite measure, including symptomatic DVT or PE, arterial thrombosis, acute cardiovascular events, or otherwise unexplained sudden death, during the first 6 months after randomization. The incidence of the composite end point was not statistically different, with 2.3% in the aspirin arm and 1.2% in the LMWH arm. The incidence of DVT was 1.1% and 1.2%, respectively, and the incidence of PE was 1.7% and 0%, respectively. No patients in either treatment arm experienced arterial thrombosis, acute cardiovascular events, or sudden death.[160] No major bleeding events occurred in either treatment arm; minor bleeding (involving the gastrointestinal tract) was reported in 1 patient (<1%) in the LMWH arm. As in the case with the aforementioned phase III study of thromboprophylaxis in patients treated with

thalidomide-containing regimens, the current study only included patients at standard risk for developing VTE, who had no clear indication or contraindications for antiplatelet or anticoagulation therapy.[160] Nevertheless, LMWH seemed to be more effective in preventing PE in this patient population. The investigators from this trial suggested that LMWH was preferred for thromboprophylaxis in patients at high risk for VTE during induction therapy with lenalidomide-containing regimens; in patients at lower risk (having no or only 1 risk factor for VTE), aspirin may be an alternative option. In addition, the investigators concluded that aspirin may also be a feasible thromboprophylaxis option during consolidation or maintenance therapy with lenalidomide.[160]

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

With respect to other ambulatory patients with cancer, the panel suggests discussing the risks and benefits of thromboprophylaxis in individuals considered to be at high risk of VTE based on an assessment of VTE risk factors (see VTE-A 1 of 3, page 1406). Some patients undergoing chemotherapy are at increased risk for developing VTE. A predictive model for chemotherapy-associated VTE has been developed[22] and independently validated in several studies. The Khorana model considers the following parameters to determine the overall risk for VTE in patients with cancer: site of primary cancer ("very high risk" for stomach or pancreatic cancer; "high risk" for lymphoma, lung, gynecologic, bladder, or testicular cancer), increased prechemotherapy platelet count (≥ 350 × 10^9/L), decreased hemoglobin level (<10 g/dL) or use of ESAs, increased prechemotherapy leukocyte count (>11 × 10^9/L), and high body mass index (≥35 kg/m^2).[22] Using a scoring system that assigns risk points to each of the above parameters, patients with 0 points (none of the risk parameters) are categorized as low risk, those with a total of 1 or 2 points are categorized as intermediate risk, and those with a total score of 3 or higher are considered high risk for developing VTE (see VTE-A 3 of 3, page 1408). In the original study by Khorana et al,[22] the rate of symptomatic VTE in the derivation cohort was 0.8%, 1.8%, and 7.1% for the low-, intermediate-, and high-risk categories, respectively. In the validation cohort, the rates were 0.3%, 2%, and 6.7%, respectively. Subsequent independent studies evaluated the utility of the Khorana scoring system in patients with cancer. Retrospective studies in patients with solid tumors and malignant lymphomas reported symptomatic VTE rates of 5% in low-risk, 16% in intermediate-risk and 27% to 41% in the high-risk patient categories.[161,162] In a more recent prospective study in patients with cancer (N=819), the rates of symptomatic VTE based on the Khorana scores were 3.8% for low-risk, 9.6% for intermediate-risk, and 17.7% for high-risk patient groups.[46]

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 (ie, nadroparin) compared with the placebo arm.[163] Furthermore, in the randomized CONKO-004 trial, the symptomatic VTE rate for patients with pancreatic cancer receiving chemotherapy was significantly reduced at 3 and 12 months with enoxaparin thromboprophylaxis (1 mg/kg daily for 3 months followed by 40 mg daily for 3 months) compared with no LMWH.[164] Most recently, a large phase III randomized placebo-controlled trial (SAVE-ONCO) in patients with advanced cancer receiving chemotherapy (N=3212) compared thromboprophylaxis with the investigational ultra-LMWH semuloparin, 20 mg daily, versus placebo.[165] The primary efficacy end point of this study was a composite end point comprising symptomatic DVT, nonfatal or fatal PE, and other death related to VTE. The main safety end point was clinically relevant bleeding events. The most common primary cancer sites were lung (37%) and colorectal (29%). Thromboprophylaxis was associated with a significant decrease in the primary end point compared with placebo (1.2% vs 3.4%; hazard ratio, 0.36; 95% CI, 0.21–0.60; P<.001).[165] The benefit of thromboprophylaxis was observed for both symptomatic DVT (0.7% vs 2.1%; hazard ratio, 0.32) and nonfatal or fatal PE (0.6% vs 1.5%; hazard ratio, 0.41). Clinically relevant bleeding (2.8% vs 2.0%) and major bleeding events (1.2% vs 1.1%) with semuloparin versus placebo were not different. Survival outcomes were not significantly different between study arms,

with deaths occurring in 43.0% and 44.5% of patients in the semuloparin and placebo arms, respectively.[165] Notably, semuloparin is an investigational agent and has not been approved by the FDA for any indication.

Patients with cancer at high risk for VTE (based on Khorana risk assessment score 3 or higher[22]) could be considered for outpatient VTE prophylaxis on an individual basis. For these patients, the panel recommends discussions with patients/caregivers regarding the potential risks and benefits of administering VTE prophylaxis in the outpatient setting. However, thromboprophylaxis in most cancer outpatients receiving chemotherapy is controversial, and its broader application using the Khorana risk assessment model or the Vienna risk assessment model should await the results of randomized controlled trials evaluating the efficacy of risk-adjusted thromboprophylaxis based on these models.[166]

Mechanical Prophylaxis

IPC devices and GCS are mechanical prophylaxis options that are principally used in patients with contraindications to pharmacologic prophylaxis, or in conjunction with pharmacologic agents in patients at very high risk of VTE. Mechanical prophylaxis should not be used in patients with an acute DVT or in the setting of severe atrial insufficiency (the latter pertains to GCS); in addition, consideration of risks and benefits should be weighed in the presence of large hematomas, thrombocytopenia (platelet count <20,000/mcL), skin ulceration or wounds (which may be more of a concern with GCS), mild arterial insufficiency (which pertains to GCS only), or peripheral neuropathy (which pertains to GCS only; see VTE-B, page 1409). 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 the use of anticoagulation therapy in VTE prevention.[76] Most of the data on the effectiveness of mechanical prophylaxis have come from surgical populations. For example, in a study comparing the VTE rate in patients undergoing gynecologic oncology surgery receiving either low-dose heparin 3 times a day (starting with the day before surgery and continuing for ≥7 days after surgery) or IPC of the calf, no difference was seen between the modalities.[167] A retrospective evaluation of high-risk patients undergoing colorectal surgery who had received mechanical prophylaxis without anticoagulant therapy indicated that IPC devices were effective in preventing postoperative VTE.[168] 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 was 14-fold higher in patients with cancer than in those with benign disease (4.1% vs 0.3%, respectively).[150] A recent multicenter, open-label, randomized, controlled trial in immobile patients with acute stroke (N=2876) found that IPC significantly reduced the odds of proximal DVT (odds ratio, 0.65; 95% CI, 0.51–0.84; *P*=·001) compared with no IPC.[169] Although this study did not enroll patients with cancer, it represents the largest study of IPCs in nonsurgical patients and provides some evidence to suggest possible benefit in nonsurgical populations. However, IPC devices should only be used alone for VTE prophylaxis in patients for whom anticoagulant prophylaxis is contraindicated.

GCS have been demonstrated to significantly reduce VTE compared with no prophylaxis and to provide even greater protection when combined with other preventive therapies.[170] However, many of these studies were conducted more than a decade ago and used fibrinogen uptake scans as a primary outcome measure, which is a now antiquated diagnostic method. In addition, very few of the patients were noted to have malignancies. Furthermore, a randomized controlled trial in patients undergoing hip surgery found that GCS did not provide significant additive protection against VTE in patients receiving fondaparinux, 2.5 mg daily for 5 to 9 days, suggesting that GCS may not have significant clinical benefits in patients able to receive more potent forms of VTE prophylaxis.[171] Similarly, results from the CLOTS1 trial, which randomly assigned patients within 1 week of stroke to routine care with or without GCS, found that GCS did not reduce the incidence of DVT in these patients, and was associated with a 4-fold increase in the frequency of skin ulcers and necrosis.[125] However, the patient group studied in the CLOTS1 trial differs considerably from the patient population described in these guidelines. Furthermore, the long delay in the institution of prophylaxis and the prolonged duration of GCS use (up to 30 days in >70%) indicate that the safety and efficacy of GCS may be different in different populations studied under different con-

ditions. Therefore, further investigation is warranted. Until more data become available, GCS should not be relied on as the sole method of VTE prophylaxis in patients with cancer.

Summary

VTE remains an important cause of morbidity and mortality among patients with cancer. Therefore, it is critical to recognize the various risk factors for VTE in patients with cancer and to identify patients who may benefit from measures to prevent VTE and its complications. The panel recommends thromboprophylaxis for all hospitalized patients with cancer who do not have contraindications to anticoagulation. A high proportion of VTE occurs in the outpatient cancer setting, which underscores the need to better identify patient populations who should be considered for outpatient thromboprophylaxis. In the outpatient setting, it is recommended that patients with cancer at elevated risks for VTE (eg, surgical settings; patients with multiple myeloma receiving certain antitumor regimens) continue to receive VTE prophylaxis with the duration of anticoagulation or antiplatelet therapy determined by the clinical situation. Risk assessment tools such as the Khorana scoring system also help identify patients in the ambulatory setting for whom discussions on the potential benefits and risks of thromboprophylaxis would be appropriate.

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