Cancer-Associated Venous Thromboembolic Disease, Version 2.2021

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ABSTRACT

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Associated Venous Thromboembolic Disease focus on the prevention, diagnosis, and treatment of patients with cancer who have developed or who are at risk for developing venous thromboembolism (VTE). VTE is a significant concern among cancer patients, who are at heightened risks for developing as well as dying from the disease. The management of patients with cancer with VTE often requires multidisciplinary efforts at treating institutions. The NCCN panel comprises specialists from various fields: cardiology, hematology/hematologic oncology, internal medicine, interventional radiology, medical oncology, pharmacology/pharmacy, and surgery/surgical oncology. This article focuses on VTE prophylaxis for medical and surgical oncology inpatients and outpatients, and discusses risk factors for VTE development, risk assessment tools, as well as management methods, including pharmacological and mechanical prophylactics. Contraindications to therapeutic interventions and special dosing, when required, are also discussed.


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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Cancer-Associated 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 Cancer-Associated Venous Thromboembolic Disease Panel members can be found on page 1201. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in cancer patients. Results from a recent population-based cohort study showed that the presence of cancer increased the risk for VTE by 9-fold. In a health claims database analysis of cancer patients undergoing chemotherapy, VTE occurred in 12.6% of patients during the 12-month period from initiation of chemotherapy, compared with a rate of 1.4% among age- and gender-matched control cohort without cancer. Chemotherapy, antiangiogenic therapy, protein kinase inhibitors and immunotherapy have all been shown to increase the risk of VTE. More importantly, thrombosis is the leading cause of death in cancer patients, second only to cancer itself. Multiple studies have reported significantly higher mortality and reduced overall survival among cancer patients who developed VTE compared with those who did not. Specifically, the occurrence of VTE has been reported to increase the likelihood of death for cancer patients by 2- to 6-fold. VTE has been reported to be the most common cause of death at 30-day follow-up among cancer patients undergoing surgery. Thus, cancer-associated VTE is a critical concern for oncology patients and healthcare providers at large.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Associated Venous Thromboembolic Disease present strategies to prevent and treat VTE in adult patients with either a diagnosis of cancer or for whom cancer is clinically suspected. The guidelines include VTE prophylaxis, VTE workup and treatment, perioperative management, as well as heparin-induced thrombocytopenia (HIT). We define VTE broadly to include acute superficial vein thrombosis, acute deep venous thrombosis (DVT), acute pulmonary embolism (PE), and splanchnic vein thrombosis (SPVT).

The underlying etiology of cancer-associated VTE is multifaceted and attributable to patient-related, cancer-related, and treatment-related factors. Stratification of these factors and accurate identification of cancer patients at risk for developing VTE are important to prevent potentially deadly complications. It has also been acknowledged that medical and surgical oncology patients, both hospitalized and ambulatory, are at increased risk of developing VTE. Therefore, appropriate use of VTE prophylaxis can bring about substantial benefits in patients at-risk. The different subtypes of VTE, despite sharing similarities, can have vastly different symptoms and prognoses, requiring customized management plans with the suitable diagnostic tools and therapeutics. There are many treatment options for VTE, encompassing anticoagulants, thrombolytics, mechanical devices and surgical procedures, with their own pros and cons. Careful selection of treatment methods with the optimal efficacy to safety consideration is instrumental in achieving the best outcomes. The NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease outline iterative implementations of therapeutic measures based on risk assessment, diagnoses of VTE subtypes, contraindications to therapeutic interventions, and cancer and treatment status of the patient.

Literature Search Statement

For each update to these NCCN Guidelines, an electronic search of the PubMed database was performed to obtain key literature. The search results were narrowed by selecting studies in adult patients published in English. Articles were also excluded if they (1) involved investigational agents that have not yet received U.S. Food and Drug Administration (FDA) approval; (2) did not pertain to the disease site; (3) were clinical trial protocols; or (4) were reviews that were not systematic reviews. The search results were further narrowed by selecting publications reporting clinical data, meta-analyses and systematic reviews of clinical studies, and treatment guidelines developed by other organizations. The potential relevance of the PubMed search results was examined by the oncology scientist and panel chair, and a list of selected articles was sent to the panel for their review and discussion at the panel meeting. The panel also reviewed and discussed published materials referenced in institutional review comments or provided with submission requests. The Discussion section was developed based on review of data from peer-reviewed publications as well as articles from additional sources deemed as relevant to these guidelines and/or discussed by the panel (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available at NCCN.org.

VTE Risk Assessment in Patients With Cancer

VTE risk factors in patients with cancer can be grouped into 3 general categories: patient-related factors, cancer-related factors, and treatment-related factors. For an individual patient with cancer, VTE risk factors in all 3 categories are likely to be present (Table 1), and the VTE risk conferred by a single risk factor cannot be evaluated in isolation from the others.

Patient-Related Factors

More advanced age, a common characteristic of many patients with cancer, was shown to be associated with an increased risk for VTE in some clinical settings. In addition, obesity has been identified as a risk factor for VTE. Other modifiable risk factors for VTE are...
smoking/tobacco use and level of physical activity. There might be confounding factors such as other smoking-attributable diseases and higher BMI in the association between smoking and VTE. Moreover, the relationship between level of physical activity and VTE is not straightforward, with multiple studies reporting a U-shaped association between the 2 entities.

A number of other patient-related VTE risk factors, although not exclusive to patients with cancer, are commonly found. These risk factors include familial and/or acquired hypercoagulability (eg strong thrombophilia such as antiphospholipid syndrome, pregnancy) and other medical comorbidities, such as infection. Although factor V Leiden and prothrombin gene 20210 mutations are found. These inherited risk factors were not associated with an increased risk for VTE among patients with cancer.

With regards to medical comorbidities, a population-based case-control study reported an estimated VTE incidence rate increase of 3-fold within the first 3 months after infection. Other noteworthy independent risk factors for VTE development include renal disease, pulmonary disease, congestive heart failure, arterial thromboembolism, and arterial thromboembolism. A history of prior VTE has also been identified as an independent risk factor for developing a subsequent VTE. 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, receiving anticoagulant treatment.

Other patient-related characteristics that are considered major risk factors for VTE development include hospitalization, prolonged immobilization, and poor performance status. These factors can also be considered treatment-related, if they result from cancer-related treatments. According to the United States CDC, between 2007 and 2009, VTE was reported in more than 547,000 hospitalized patients annually, with more than 28,700 deaths. Moreover, 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.

### Cancer-Related Factors

Several VTE risk factors are exclusive to patients with cancer, including the presence of malignancy, type and stage of cancer. As established in the Overview (page 1182), cancer is a significant risk factor for VTE, and causes approximately 20% of VTE cases seen in the community. Additionally, several studies have evaluated the association between types of cancer and the risk for developing VTE. Pancreatic cancer and brain tumors are consistently associated with a high risk for VTE. It has been postulated that the tissue factor expression that occurs early in malignant transformation of the pancreas in association with angiogenesis and may be predictive of VTE in pancreatic cancer. Although differences in study designs make it difficult to compare VTE rates according to a specific type of malignancy,
other cancers that have been associated with an increased risk for VTE include cancers of the stomach, kidney, uterus, lung, ovary, bladder, and testis. In contrast, breast cancer was associated with a relatively low VTE risk in some studies. Nevertheless, due to the relatively high prevalence of breast cancer, VTE in patients with breast cancer is not uncommon.

An increased risk for VTE has also been observed in certain hematologic malignancies, such as lymphoma, acute leukemia, and multiple myeloma (for guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma, available at NCCN.org). Notably, patients with high-grade lymphoma and acute promyelocytic leukemia appear to be at higher risk of VTE than patients with other forms of lymphoma or leukemia. Furthermore, in a study of patients with high-grade non-Hodgkin lymphoma, disease-related venous compression was shown to be the most common cause of VTE. Thus, the mechanisms for VTE development in hematologic malignancies can differ from those in solid tumors and are worth further investigation.

In addition, advanced disease stages and distant metastases increase VTE risk. For example, Blom et al reported an adjusted odds ratio (OR) of 19.8 for VTE risk in patients with solid tumor cancer with distant metastases compared with patients without. However, the strength of associations can differ substantially between cancer types, with the highest incidence rate difference for VTE according to stages reported for pancreatic cancer and the lowest rate reported for prostate cancer, respectively.

**Treatment-Related Factors**

Treatment-related VTE risk factors include major surgery, the presence of a central venous access device (CVAD, also known as a catheter), and administration of systemic therapies. Heit et al reported nearly 22-fold increase in the risk for VTE development in patients hospitalized for recent surgery compared with those who had not been hospitalized or had not undergone recent surgery. The overall 30-day VTE rate in patients with cancer after major surgeries ranges from 1.8% to 13.2%, with esophageal resection patients having the highest rate of 13.2% (95% CI, 8.8%–18.9%). Importantly, a significant proportion of VTE episodes (34%) among surgical oncology
patients are diagnosed after hospital discharge, highlighting the importance of extended VTE prophylaxis in this patient population.80

CVAD has been identified as a risk factor for the development of upper-extremity DVT.81–84 Besides, hematopoietic stem cell transplantation is a common procedure among individuals with hematologic malignancies and has been associated with increased VTE risk, principally due to catheter usage.85 The association between CVAD and VTE may be the result of venous stasis and vessel injury after insertion of the CVAD86,87 or infections as a result of catheter placement.88,89 One study identified more than one insertion attempt and previous CVAD insertion as significant risk factors for CVAD-related thrombosis, supporting the hypothesis that vessel wall trauma or endothelial damage contribute to this phenomenon.84

Many agents used in cancer treatment are also associated with an increased risk for developing VTE, notably systemic therapy (chemotherapy, protein kinase inhibitors, immunotherapy), hormone therapy with estrogenic compounds, and antiangiogenic agents. The association of systemic therapy with VTE in patients with cancer has been shown in several studies.2,26,82,90,91 In one population-based case-control study, the ORs for development of VTE were 6.5 and 4.1 for patients with cancer receiving chemotherapy and those not receiving chemotherapy, respectively.82 It was estimated that the annual incidence of VTE could be as high as 15% in patients with colorectal cancer treated with chemotherapeutic regimens.91 There is also evidence that prechemotherapy thrombocytosis,26,43,90 leukocytosis,26 and hemoglobin level,10 g/dL26,90 are predictive of VTE in patients receiving chemotherapy, although the association of anemia with VTE may be complicated by the use of erythropoietic stimulating agents (ESAs).

Exogenous hormonal compounds, such as selective estrogen receptor modulators (eg, tamoxifen, raloxifene for breast cancer) can lead to increased VTE risk.92–96 Diethylstilbestrol phosphate used in combination with doxorubicin for the treatment of hormone-refractory prostate cancer was reported to increase VTE risk compared with doxorubicin alone.97 Use of hormonal compounds, such as hormone replacement therapy98–99 or hormonal contraceptive agents,100–102 have also been associated with increased risk for developing VTE. VTE risks may vary between different formulations of combined oral contraceptives, depending on the type of progestogen used.101,103,104 Additionally, progestin-only
**CONTRAINDICATIONS TO VTE PROPHYLAXIS**

**Contraindications to Prophylactic Anticoagulation**

- Active bleeding
- Thrombocytopenia (platelet count <50,000/µL or clinical judgment)
- Underlying hemorrhagic coagulopathy (eg, abnormal PT or aPTT excluding a lupus inhibitor/anticoagulant) or known bleeding disorder in the absence of replacement therapy (eg, hemophilia, von Willebrand disease)
- Indwelling neuraxial catheters (contraindication for apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban, or enoxaparin dose exceeding 40 mg daily)
- Neuraxial anesthesia/lumbar puncture
- Interventional spine and pain procedures

**Contraindications to Mechanical Prophylaxis**

- Absolute
  - Acute DVT (unless on therapeutic anticoagulation)
  - Severe arterial insufficiency (pertains to graduated compression stockings [GCS] only)
  - Relative
    - Large hematoma
    - Skin ulcerations or wounds
    - Mild arterial insufficiency (pertains to GCS only)
    - Peripheral neuropathy (pertains to GCS only)

1 For agent-specific contraindications, see Anticoagulant Options: Contraindications and Warnings (VTE-D, 3 of 4*).
2 In patients at high risk, prophylactic anticoagulation may be appropriate even if platelet count is low as 25,000/µL. See Management of Anticoagulation for VTE in Patients with Chemotherapy-Induced Thrombocytopenia (VTE-F*).
3 Refer to institutional-specific anesthesia practice guidelines, if available. Twice-daily prophylactic dose UFH (5000 units every 12 h) and once-daily LMWH (eg, enoxaparin 40 mg once daily) may be used with neuraxial anesthesia. Twice-daily prophylactic dose LMWH (eg, enoxaparin 30 mg every 12 h), prophylactic dose fondaparinux (2.5 mg daily), and therapeutic dose anticoagulation should be used with extreme caution with neuraxial anesthesia. The safety of thrice-daily prophylactic dose UFH in conjunction with neuraxial anesthesia has not been established. (Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy. American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines [Third Edition]. Reg Anesth Pain Med 2010;35:64-101.)
4 Timing of LMWH: For LMWH, placement or removal of a neuraxial catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of DVT. Longer delays (24 h) are appropriate to consider for patients receiving therapeutic doses of LMWH. A post-procedure dose of LMWH should usually be given no sooner than 4 hours after catheter removal. (FDA Drug Safety Communication. Updated recommendations to decrease risk of spinal column bleeding and paralysis in patients on low molecular weight heparins. November 6, 2013: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM373735.pdf.) In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.
6 Skin ulcerations and wounds are more common with the use of GCS.

**Risk Assessment in Cancer Outpatients**

A predictive model for chemotherapy-associated VTE was published by Khorana et al,26 which has been reproduced and adapted in the NCCN Guidelines for Cancer-associated Venous Thromboembolic Disease as a risk assessment tool for cancer outpatients (see VTE-C, page 1192). The association of VTE with 5 readily available clinical and laboratory variables was characterized in a derivation cohort of 2,701 cancer outpatients from a prospective observational study. A risk model was derived and validated in an independent cohort of 1,365 patients from the same study. 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 BMI (≥35 kg/m^2).26 Using a scoring system that assigns risk points to each of the above parameters, patients with 0 points (none of the above risk parameters) are categorized as low risk, those with a total of 1 or 2 points are categorized as intermediate risk, and those with a total score of 3 or higher are considered high risk of developing VTE.

This risk assessment model was externally validated by several retrospective and prospective studies; however, reported rates for developing VTE based on the 3 risk categories vary widely because of differences in...
patient populations and follow-up periods. In the original study, the rate of symptomatic VTE in the derivation cohort was 0.8%, 1.8%, and 7.1% for the low-, intermediate-, and high-risk categories, respectively. In the validation cohort, the rates were 0.3%, 2%, and 6.7%, respectively. An analysis of 1,412 patients from phase I studies with a comparable duration of follow-up reported rates of 1.5%, 4.8%, and 12.9% for each of the risk categories, respectively. This study also identified the risk assessment score to be the only predictor of VTE. These rates are thus summarized and reported as part of the risk assessment tool for cancer outpatients (see VTE-C, page 1192).

The risk assessment model by Khorana et al was also validated and extended by Ay and colleagues, 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, so their inclusion in routine thrombotic risk assessment should be predicated upon their validation in future studies. In addition to the Vienna CATS risk assessment model, several other risk assessment models have been published including the Protecht score, the CONKO score, and the COMPASS CAT model. A prospective multicenter study of the Khorana score, the Vienna CATS score, the Protecht score and the CONKO score found that the discriminatory performance of these models was modest (C-statistics from 0.50 to 0.57). This study has been criticized because only 25% (230 of 876) of participants were enrolled at the start of chemotherapy, the highest risk period for VTE. Thus far, only the Khorana score has been successfully used in prospective randomized trials of thromboprophylaxis to identify at risk patients.

VTE Prophylaxis in Patients With Cancer

It has been acknowledged by clinical practice guidelines and data from numerous clinical trials that the appropriate use of VTE prophylaxis is safe and effective. Despite this, results of practice surveys indicate that VTE prophylaxis is perhaps still under-used. The Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey noted that only 50% of surgical oncologists and 5% of medical oncologists routinely used VTE prophylaxis in patients with cancer. Similar results were documented in the multinational IMPROVE and ENDORSE registries of hospitalized medically ill patients in which

### VTE PROPHYLAXIS OPTIONS FOR HOSPITALIZED MEDICAL ONCOLOGY PATIENTS (VTE-1)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Standard Dosing</th>
<th>Renal Dose</th>
<th>Obesity Dosing (BMI ≥40 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>5,000 units SC daily (category 1)</td>
<td>Avoid if CrCl &lt;30 mL/min</td>
<td>Consider 7,500 units SC daily OR 5,000 units SC every 12 hours OR 40–75 units/kg SC daily</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg SC daily (category 1)</td>
<td>Recommend 30 mg SC daily if CrCl &lt;30 mL/min</td>
<td>Consider 40 mg SC every 12 hours OR 0.5 mg/kg SC daily</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg SC daily (category 1)</td>
<td>Caution if CrCl 30–49 mL/min</td>
<td>Consider 5 mg SC daily</td>
</tr>
<tr>
<td>Unfractionated Heparin (UFH)</td>
<td>5,000 units SC every 8–12 hours (category 1)</td>
<td>Same as standard dose</td>
<td>Consider 7,500 units SC every 8 hours</td>
</tr>
</tbody>
</table>

CrCl = estimated creatinine clearance; SC = subcutaneous
only 45% of patients with cancer received any form of VTE prophylaxis. The NCCN Panel recommends identification of patients at risk for developing VTE and subsequent initiation of VTE prophylaxis based on inpatient/outpatient and medical/surgical oncology patient status.

The panel does not recommend VTE prophylaxis for patients with cancer based only on the presence of a CVAD due to the lack of data establishing the efficacy of prophylactic doses of low-molecular-weight heparin (LMWH) or warfarin in this group of patients.

Inpatient VTE Prophylaxis

At-Risk Population

Hospitized patients with cancer are at high risk for VTE. NCCN Guidelines for Cancer-associated Venous Thromboembolic Disease recommends VTE prophylaxis for all adult medical and surgical inpatients with a diagnosis of cancer or clinical suspicion of cancer. Although multiple risk assessment models have been developed for hospitalized medical and surgical patients, none of them have been validated in prospective management studies for hospitalized patients with cancer. Therefore, providers are encouraged to discuss VTE risk factors, risks and benefits of VTE prevention, and the importance of patient adherence to care programs prior to the initiation of VTE prophylaxis.

Adult inpatients with cancer should undergo the following evaluation prior to the initiation of thromboprophylaxis: comprehensive medical history and physical examination, CBC with platelet count and differential, prothrombin time, activated partial thromboplastin time (aPTT), and comprehensive metabolic panel including liver and kidney function tests. In addition to these components, initial workup for inpatient VTE prophylaxis also includes a VTE and bleeding risk assessment.

Initial prophylaxis

In case of no contraindication to anticoagulation (see VTE-A, page 1186), prophylactic anticoagulation therapy is recommended (category 1). The recommendation assumes that ambulation in hospitalized patients with cancer is inadequate to reduce VTE risk. Preoperative dosing with LMWH or unfractionated heparin (UFH) for high-risk surgery (eg, abdominal/pelvic patients) can be considered with or without intermittent pneumatic compression (IPC) device.
### VTE PROPHYLAXIS OPTIONS FOR HOSPITALIZED SURGICAL ONCOLOGY PATIENTS (VTE-1)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Standard Dosing</th>
<th>Renal Dose</th>
<th>Obesity Dosing (BMI ≥40 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin¹,²,³,⁴</td>
<td>5,000 units SC the evening prior to surgery, then 5,000 units SC daily OR 2,500 units SC 1–2 hours prior to surgery and 2,500 units SC 12 hours later then 5,000 units SC daily OR beginning post-op Day 1</td>
<td>Avoid if CrCl &lt;30 mL/min</td>
<td>Consider 7,500 units SC daily OR 5,000 units SC every 12 hours OR 40–75 units/kg SC daily</td>
</tr>
<tr>
<td>Enoxaparin³,⁴,⁵,⁶</td>
<td>40 mg SC 10–12 hours prior to surgery then 40 mg SC daily or 40 mg SC daily with first dose 6–12 hours post operation</td>
<td>Recommend 30 mg SC daily if CrCl &lt;30 mL/min</td>
<td>Consider 40 mg SC every 12 hours</td>
</tr>
<tr>
<td>Fondaparinux³,⁵,⁶,⁷,⁸</td>
<td>2.5 mg SC daily no earlier than 6–8 hours post-operation Avoid in patients weighing &lt;50 kg</td>
<td>Caution if CrCl 30–49 mL/min Avoid if CrCl &lt;30 mL/min</td>
<td>Consider 5 mg SC daily</td>
</tr>
<tr>
<td>UFH¹³,¹⁴,¹⁵</td>
<td>5,000 units SC 2–4 hours prior to surgery then 5,000 units SC every 8 hours through post-operative day 1</td>
<td>Same as standard dose</td>
<td>Consider 7,500 units SC every 8 hours post-operation</td>
</tr>
<tr>
<td>Apixaban³,⁴,¹⁶</td>
<td>UFH 5,000 units SC 30 minutes prior to surgery and every 8 hours through post-op Day 1 then apixaban 2.5 mg PO every 12 hours</td>
<td>Avoid if CrCl &lt;30 mL/min</td>
<td>No dose adjustment available</td>
</tr>
</tbody>
</table>

CrCl = estimated creatinine clearance, SC = subcutaneous; PO = oral

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### Medical Oncology Patients

Anticoagulant options for VTE prophylaxis of hospitalized medical oncology patients are listed in algorithm (see VTE-B 1 of 5, page 1187). LMWHs (dalteparin¹⁴¹–¹⁴³ and enoxaparin¹⁴⁴–¹⁴⁷), fondaparinux¹⁴⁸–¹⁵⁰ and UFH¹⁴⁹,¹⁵¹ are category 1 options for this group of patients. Recommendations are derived from patients hospitalized with a medical illness, most commonly congestive heart failure and acute or chronic respiratory disease, and hospitalization >6 days, immobility/bed rest ≥3 days, age ≥40 years, plus additional risk factors for VTE.¹⁵² The panel recommends that thromboprophylaxis is carried out for the duration of hospital stay or 6-14 days or until the patient is fully ambulatory. A meta-analysis of 9 randomized trials concluded that during anticoagulant prophylaxis with LMWHs, fondaparinux, or UFH, patients had significant reductions in any PE (relative risk, 0.43 [95% CI, 0.26 to 0.71]; absolute risk reduction, 0.29%); and fatal PE (relative risk, 0.38 [95% CI, 0.21 – 0.69]; absolute risk reduction, 0.25%) compared with no treatment.¹⁵²

Specifically, the PREVENT trial supported the use of fixed dose dalteparin (5,000 units daily) to prevent symptomatic VTE, fatal PE, sudden death, or asymptomatic proximal DVT in both obese (2.8% vs 4.3% with placebo; relative risk, 0.64; 95% CI, 0.32 – 1.28) and elderly patients (4.2% vs 8.0% with placebo; relative risk, 0.52; 95% CI, 0.31 – 0.87).¹⁴² These data are comparable to those from another study, which investigated dalteparin at the same dose in acutely ill medical patients and reported a reduction in VTE incidence from 4.96% in the placebo group to 2.77% in the dalteparin group (relative risk, 0.55; 95% CI, 0.38 to 0.80; P=.0015).¹⁴³ Also in patients with acute medical illnesses, enoxaparin 40 mg daily led to a significantly lower rate of VTE than placebo (5.5% vs 14.9%; relative risk, 0.37; 97.6% CI, 0.22 to 0.63; P<.001). In this study, a lower dose of enoxaparin (20 mg daily) did not have the same benefits.¹⁴⁵ Enoxaparin 40 mg daily was explored in 2 other studies, among hospitalized general medical patients and acutely ill medical patients, respectively, and did not result in a reduction in death rate over placebo.¹⁴⁶,¹⁴⁷

Results from a large randomized clinical trial in older acute medical inpatients supported prophylactic fondaparinux at 2.5 mg daily, due to significantly lower VTE rates with fondaparinux compared with placebo (5.6% vs 10.5%; relative risk reduction, 46.7%; 95% CI, 7.7%–69.3%).¹⁵⁰ Last but not least, in a randomized trial among patients with heart failure and/or chest infection, UFH at 5,000 units every 8 hours was...
determined to significantly lower the frequency of DVT in the legs (26% vs 4% with placebo; \( P < .01 \)).

Multiple studies have shown that dosing UFH 3-times per day is more effective than twice daily in preventing DVT in general surgery and medical patients.153–154

**Surgical Oncology Patients**

It is well established that low dose heparin offers an effective way of preventing VTE and VTE-related deaths in general population undergoing surgery, which also applies to the cancer population.127,155-156 Anticoagulant options for VTE prophylaxis of hospitalized surgical oncology patients are listed within the Guidelines section “VTE Prophylaxis Options” (page 1189). LMWHs (dalteparin,141,157 enoxaparin144,138), fondaparinux,129,148,159 UFH,160-163 and apixaban164 (only for gynecologic oncology patients) are recommended. Recommended doses are derived from patients undergoing planned, elective, open abdominal or pelvic surgery for malignancy (OR time > 45 minutes, age > 40 years). Thromboprophylaxis should be carried out for at least 7 to 10 days or until the patient is fully ambulatory. It must be noted that UFH led to higher rates of heparin-induced thrombocytopenia (HIT; See Guidelines section, “HIT Heparin-Induced Thrombocytopenia,” at NCCN.org), as much as 10-fold that of LMWHs like enoxaparin, in surgical patients. Efforts such as the AVOID-heparin initiatives have led to drastic reductions in HIT, a morbid and potentially fatal complication of heparin use.165

The recommended prophylactic options are presumed to be equivalent as studies have not clearly identified a particular anticoagulant regimen to have superior efficacy for the prevention of VTE in patients with cancer.128,129,163,164,166,167 These comparisons have been made in patients undergoing major abdominal surgery receiving postoperative fondaparinux versus perioperative dalteparin,130 first-generation LMWH versus UFH,160,161 enoxaparin versus UFH,162,163 dalteparin versus UFH,167 and enoxaparin versus apixaban.164 In particular, some of these studies focused exclusively on patients with cancer undergoing major surgeries for various malignancies including gynecologic neoplasms.163,164,167 In particular, apixaban prophylaxis should only apply to gynecologic oncology patients, as data for safety and efficacy are currently only available for the specific population. In the supportive study, apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed and continued for 28 days.164

### Extended VTE Prophylaxis Options for Surgical Oncology Patients (VTE-2)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Standard Dosing</th>
<th>Renal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2.5 mg PO every 12 hours x 28 days</td>
<td>Avoid if CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5,000 units SC daily x 28 days</td>
<td>Avoid if CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg SC daily x 28 days</td>
<td>Avoid if CrCl &lt;30 mL/min</td>
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CrCl = estimated creatinine clearance, SC = subcutaneous, PO = oral

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1 Apixaban is absorbed in the stomach, proximal small bowel, and colon. Patients who have had significant resections of these portions of the intestinal tracts may be at risk for sub-optimal absorption.

2 Recommendations derived from patients undergoing planned, elective, open abdominal and pelvic surgery for malignancy (OR time >45 minutes, age ≥40 years)

3 Only applies to gynecologic oncology patients. Apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed. Duration of prophylaxis was 28 days.

4 In high-risk abdominal and pelvic surgery patients (previous VTE, bed rest ≥4 days, OR time >2 hours, advanced stage disease or age ≥60), 4 weeks of thromboprophylaxis is recommended.15,17
Renal Dosing

The doses for some anticoagulants might need to be adjusted in both hospitalized medical oncology and hospitalized surgical oncology patients with renal disease. LMWHs are excreted via the kidney; due to pharmacologic and pharmacokinetic differences, there might be variation in the degree of accumulation of various LMWHs in patients with renal impairment. In the TIMI-11A trial in patients with non-ST-segment elevation acute coronary syndrome, 11 patients with renal impairment showed a reduction in enoxaparin clearance compared with those with normal renal function. Other studies have supported this observation, noting that the inverse relationship between estimated creatinine clearance (CrCl) and anti-Xa concentrations might be enoxaparin dose-dependent. In contrast to enoxaparin, dalteparin might not accumulate in patients with severe renal function. LMWH accumulation can increase the risk of major bleeding; thus, its benefits must be carefully weighed against potential complications in this subset of patients.

It has been suggested that a reduced dose of enoxaparin in patients with severe renal impairment leads to fewer major bleeding events compared with standard doses. Some studies, primarily in the setting of non-ST-segment elevation acute coronary syndrome, comparing the efficacy and safety of enoxaparin versus UFH or enoxaparin versus fondaparinux have found no clinically meaningful difference between these options in patients with renal impairment. The NCCN panel recommends that in patients with severe renal disease (CrCl <30 mL/min), dalteparin, fondaparinux, and apixaban should be avoided and UFH should be used instead. If enoxaparin is used, it should be dose at 30 mg subcutaneously once daily. In those with moderate renal disease (CrCl 30-49 mL/min), fondaparinux should be used with caution.

Obesity Dosing

It has been suggested that fixed doses of anticoagulants might not be sufficient in obese patients. Due an inverse correlation between anti-Xa levels and body weight after a fixed dose of prophylactic anticoagulant, patients at extremes of body weight may not develop adequate anti-Xa levels for maximal anticoagulant effectiveness. Although there are limited data available to support dosing recommendations for patients with cancer with BMI ≥40kg/m², the NCCN panel suggests consideration of increased prophylactic anticoagulation doses in obese hospitalized medical and surgical oncology patients.
The pharmacodynamic and clinical studies supporting these recommended dosing regimens have been carried out primarily in gastric bypass surgery patients receiving prophylactic dalteparin (7,500 units daily,\textsuperscript{184} 5,000 units every 12 hours,\textsuperscript{185} or 40 – 75 units/kg daily\textsuperscript{186}), enoxaparin (40 mg every 12 hours\textsuperscript{179} –\textsuperscript{194} or 0.5 mg/kg daily\textsuperscript{195} –\textsuperscript{197}), fondaparinux (5 mg daily\textsuperscript{198}), and UFH (7,500 units every 8 hours\textsuperscript{191}). Prospective investigations in the oncology population of these dosing regimens are warranted to further ascertain their efficacy for obese patients.

Mechanical Prophylaxis

In case of contraindication to anticoagulation, mechanical prophylaxis is recommended (for contraindications to mechanical prophylaxis, see VTE-A, page 1186). Most data regarding the use of mechanical prophylaxis come from studies of surgical or stroke patients and have been extrapolated to the medical population.\textsuperscript{199} –\textsuperscript{201} According to one of these studies, no difference was seen in the VTE rate in gynecologic oncology surgery patients receiving either low-dose heparin or IPC of the calf, even though the former was more frequently associated with postoperative bleeding complications.\textsuperscript{199} Additionally, in contrast to graduated compression stockings (GCS), IPC significantly reduced DVT and was associated with a lower risk of skin complications.\textsuperscript{201} –\textsuperscript{202} However, IPC might not be an equivalent substitute for anticoagulants in all scenarios. Results from a retrospective study of patients who had undergone abdominal surgery for gynecologic cancers and received pneumatic compression showed that the incidence of PE in patients with cancer (4.1%) exceeded by 14-fold that in patients with benign disease (0.3%).\textsuperscript{203} Additionally, results from a randomized trial (including a limited number of patients with cancer) suggest that addition of mechanical prophylaxis to pharmacologic prophylaxis in critically ill patients may not reduce the incidence of DVT.\textsuperscript{204} Other disadvantages of IPC include the potential for interference with ambulation and the need to keep the devices in place nearly continuously until patients are fully ambulatory. Therefore, IPC devices should only be used alone for VTE prophylaxis when anticoagulant prophylaxis is contraindicated.

GCS is an alternative mechanical prophylactic method that might provide benefit in VTE reduction, especially when combined with other therapies.\textsuperscript{205} However, similar to IPC, it should not be relied as the sole method of VTE prophylaxis in patients with cancer. First, many studies demonstrating its efficacy were conducted more than a

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\textsuperscript{2} Khorana AA. Cancer and Coagulation. Am J Hematol 2012;87 Supp 1:S82-87.

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### VTE RISK ASSESSMENT IN CANCER OUTPATIENTS

#### Khorana Predictive Model for Chemotherapy-Associated VTE\textsuperscript{1}

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Score</th>
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<tr>
<td>Site of primary cancer</td>
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</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count 350 x 10(^3)L or higher</td>
<td>1</td>
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<tr>
<td>Hemoglobin level less than 10 g/dL or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count higher than 11 x 10(^9)L</td>
<td>1</td>
</tr>
<tr>
<td>BMI 35 kg/m(^2) or higher</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Total Score | Risk Category | Risk of Symptomatic VTE\textsuperscript{2} |
<table>
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<tr>
<td>0</td>
<td>Low</td>
<td>0.3–1.5%</td>
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<tr>
<td>1, 2</td>
<td>Intermediate</td>
<td>2.0–4.8%</td>
</tr>
<tr>
<td>3 or higher</td>
<td>High</td>
<td>6.7–12.9%</td>
</tr>
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\textsuperscript{2} Khorana AA. Cancer and Coagulation. Am J Hematol 2012;87 Supp 1:S82-87.
decade ago and used fibrinogen uptake scans as a primary outcome measure—a now antiquated diagnostic method. Additionally, a randomized controlled trial in patients undergoing hip surgery found that GCS did not provide significant additive protection against VTE in patients receiving fondaparinux. Similarly, results from the CLOTS1 trial in stroke patients found that GCS did not reduce the incidence of DVT and was associated with a 4-fold increase in the frequency of skin ulcers and necrosis. In addition, the GAPS study noted that pharmacologic VTE prophylaxis was noninferior to pharmacologic prophylaxis combined with GCS, therefore GCS may be unnecessary in surgical patients receiving pharmacological thromboprophylaxis. It should be noted that most of these trials either did not include patients with cancer or only included a minority of patients with cancer. Thus, GCS should only be used when prophylactic anticoagulants are contraindicated.

Overall, clinicians should discuss VTE prevention and the risks/benefits of pharmacologic and mechanical VTE prophylaxis with their patients. A systematic approach to patient risk assessment is recommended. Institutions are strongly encouraged to implement best practice programs to monitor provider and patient adherence to VTE prophylaxis.

**VTE Prophylaxis Following Discharge and for Ambulatory Patients With Cancer at Risk**

**At-Risk Population**

Certain groups of patients with cancer are known to remain at risk for VTE after discharge from the hospital. In a systematic review of VTE, 74% of patients were diagnosed in the outpatient setting, with a substantial portion having undergone surgery (23%) or hospitalization (37%) in the preceding 3 months. Furthermore, in the @RISTOS observational cohort study of general, urologic, and gynecologic cancer surgery patients, 40% of VTE events occurred later than 21 days postoperation and greatly exceeded hemorrhagic complications as a cause of death. The NCCN Panel identifies patients at risk for VTE to be all adult medical or surgical patients with a diagnosis of cancer, patients who received VTE prophylaxis during hospitalization, cancer inpatients intended for discharge, and any outpatients at risk based on VTE risk assessment. Providers are encouraged to discuss VTE risk factors, bleeding risk factors, risks and benefits of VTE prevention, and the importance of patient adherence to care programs prior to the initiation of VTE prophylaxis.

**Medical Oncology Patients**

Although there is a lack of consistent evidence to support extended outpatient prophylaxis in most populations of ambulatory medical oncology patients, it is recommended for multiple myeloma patients receiving highly thrombogenic regimens. For guidance on management of VTE in patients receiving treatment for multiple myeloma, refer to the NCCN Guidelines for Multiple Myeloma (available at NCCN.org).

The Khorana risk score can be used to assess VTE risk in other medical oncology outpatients (see VTE-C, page 1192). Those with low risk for VTE (Khorana score <2) do not need routine VTE prophylaxis. Those with an intermediate or high risk of VTE (Khorana score ≥2) should consider anticoagulant prophylaxis for up to 6 months or longer, if risk persists. Anticoagulant options for VTE prophylaxis of ambulatory medical oncology patients include direct oral anticoagulants (DOACs) (apixaban, rivaroxaban) and LMWHs (dalteparin and enoxaparin) and are listed in the algorithm (VTE-B 2 of 5, page 1188). For information on contraindications, refer to “Contraindications to VTE Prophylaxis” (VTE-A, page 1186). The recommended dosing is derived from clinical trials with high thrombosis risk ambulatory patients with cancer (>18 years, Khorana VTE Risk Score >2, initiating new course of chemotherapy) and are not included in product labeling. It must be noted that DOACs are primarily absorbed in the stomach, proximal small bowel (apixaban and rivaroxaban), and colon (apixaban only). Therefore, patients who have had significant resections of these portions of the intestinal tracts may be at risk for suboptimal absorption.

DOACs have demonstrated efficacy in preventing VTE in ambulatory patients with cancer. Specifically, the rate of VTE significantly decreased with apixaban prophylaxis versus placebo (4.2% vs 10.2%; hazard ratio [HR], 0.41; 95% CI, 0.26–0.65; P=.001). Furthermore, rivaroxaban prophylaxis yielded lower incidence of VTE compared with placebo, even though the results did not reach statistical significance (6.0% vs 8.8%; HR, 0.66; 95% CI, 0.40–1.09; P=.10). It is recommended that LMWHs be considered in patients with advanced unresectable or metastatic pancreatic cancer. In particular, dalteparin has been shown in this group of patients to significantly reduce the incidence of VTE from 23% to 3.4% (P=.002). Also in patients with pancreatic cancer, the CONKO-004 trial reported a significantly decreased rate of symptomatic VTEs in the enoxaparin group compared with the observation group (6.4% vs 15.1%; HR, 0.40; 95% CI, 0.19–0.83; P=.01).

**Other Dose Modifications for Medical Oncology Patients**

To balance bleeding risk and VTE likelihood, the NCCN Panel recommends that prophylactic anticoagulation therapy be avoided in medical oncology patients whose platelet count is less than 50,000/μL (see VTE-A, page
A reduced dose of enoxaparin can be used in those with platelet count between 50,000 and 75,000/µL.

**Surgical Oncology Patients**

The panel recommends prophylaxis for up to 4 weeks postoperation for high-risk abdominal or pelvic cancer surgery patients. These include patients undergoing surgery for gastrointestinal malignancies, those with a previous episode of VTE, anesthesia time >2 hours, perioperative bed rest ≥4 days, advanced stage disease, and age >60 years. Extended anticoagulant options for surgical oncology patients are listed in the algorithm (see VTE-B 4 of 5, page 1190). Apixaban and LMWHs (dalteparin and enoxaparin) are recommended options for this group of patients. The recommended dosing is derived from patients undergoing planned, elective, open abdominal and pelvic surgery for malignancy (surgery time >45 minutes, age ≥40 years). It was also noted in a retrospective study comparing the effectiveness of dalteparin to UFH that the dalteparin dosing regimen may not be optimal in gynecologic surgery patients. Thus, more data are needed to identify subsets of patients who might derive differential benefit from particular anticoagulant regimens.

Multiple studies have shown the clinical benefit of extended VTE prophylaxis for patients undergoing major surgeries. In a study evaluating the optimal duration of dalteparin in patients after major abdominal surgery, the cumulative incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis (7-day) to 7.3% with prolonged thromboprophylaxis (21-day; risk reduction, 55%; 95% CI, 15 – 76; P = .012). Another study in patients after abdominal or pelvic surgery for cancer showed that the rates of VTE were 12.0% in the placebo group and 4.8% in the enoxaparin group (P=.02) at 4 weeks, a significant difference that persisted at 3 months (13.8% vs 5.5%, P = .01). Data from a meta-analysis comparing prolonged thromboprophylaxis with LMWH versus control showed that the incidence of overall VTE after major abdominal or pelvic surgery was reduced from 13.2% in the control group to 5.3% in the patients receiving out-of-hospital LMWH (Mantel Haentzel OR 0.38; 95% CI, 0.26 – 0.54).

**Renal Dosing**

The rationale and guidance for anticoagulant usage in patients with renal disease is the same for oncology inpatients and outpatients. It must be noted that although apixaban should be avoided for CrCl <30 mL/min, rivaroxaban, which is only recommended for ambulatory medical oncology patients, should be avoided for CrCl <15 mL/min.

**Contraindications to VTE Prophylaxis**

**Contraindications to Prophylactic Anticoagulation**

Contraindications to anticoagulation can be relative or absolute, and temporary or permanent. Consideration of the degree of contraindication to anticoagulation and its duration are essential when evaluating the risks and benefits of anticoagulation in the individual patient (see VTE-A, page 1186).

It must be noted that 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 LMWHs and fondaparinux include boxed warnings specifying that the risk for spinal or epidural hematoma resulting in long-term paralysis is increased when these anticoagulants are administered to patients receiving epidural or spinal anesthesia or those undergoing spinal puncture. UFH should also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture. Anticoagulant prophylaxis is usually considered unsafe for platelet count less than 50,000/µL. Data on withholding or lowering doses of anticoagulants in the case of significant thrombocytopenia have been reported mostly for the treatment of VTE in retrospective cohort studies and case series of patients with hematologic malignancies.

Of note, a prolonged aPTT is not considered a contraindication to anticoagulation therapy in patients with a lupus inhibitor or lupus anticoagulant, such as those diagnosed with antiphospholipid syndrome. Antiphospholipid antibodies prolong the aPTT by interfering with the interaction between coagulation factors in the patient plasma sample and the phospholipids provided in the aPTT test reagent. Antiphospholipid antibodies have been associated with an increased risk for venous and arterial thromboembolism and adverse pregnancy outcomes. Any patient who has experienced a thrombotic event and fulfills diagnostic criteria for antiphospholipid syndrome should be considered for indefinite anticoagulation therapy.

**Contraindications to Mechanical Anticoagulation**

Whenever mechanical prophylaxis is used, steps should be taken to ensure its proper use and continuous application. Mechanical prophylaxis should not be used in patients with an acute DVT. In addition, consideration of risks and benefits should be weighed in the presence of large hematomas. It has been established earlier that skin ulceration or wounds might be a particular concern for GCS, as opposed to IPC. Other contraindications for GCS comprise of arterial insufficiency and peripheral neuropathy (due to potential skin damage). In particular, it has been shown that the
use of GCS on legs with impaired arterial flow can worsen ischemia.⁴²²

**Summary**
In the 2021 update, the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease were extensively revised to remove VTE risk assessment models and prophylaxis for multiple myeloma patients, which has now been incorporated into the NCCN Guidelines for Multiple Myeloma (available at NCCN.org). Another major change was the inclusion of detailed prophylactic anticoagulation dosing information for medical and surgical oncology patients based on their inpatient/outpatient status. In some cases, special dosing information is included for patients who are obese, who have renal disease, or who have significant thrombocytopenia. Oftentimes, dosing information is derived from nononcology populations; therefore, data from prospective randomized studies in oncology patients are sorely needed to further establish specific dosing recommendations for patients with cancer. Certain dosing recommendations are also confined to specific oncology patient subsets (ie, gynecologic cancers or pancreatic cancers), necessitating future investigations into other oncology patient populations.

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Cancer-Associated Venous Thromboembolic Disease, Version 2.2021


### Individual Disclosures for the NCCN Cancer-Associated Venous Thromboembolic Disease Panel

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John Fanikos, RPH, MBA: Hospital Quality Foundation, and North American Thrombosis Forum

Krishna Gundabolu, MD: Genentech Corporation

*The NCCN Guidelines Staff have no conflicts to disclose.*