Cancer-Associated Venous Thromboembolic Disease, Version 2.2021

Michael B. Streiff, MD[1,*]; Bjorn Holmstrom, MD[2]; Dana Angelini, MD[3]; Aneel Ashrani, MD, MS[4]; Amro Elshoury, MD[5]; John Fanikos, RPH, MBA[6]; Kleber Yotsumoto Fertrin, MD, PhD[7]; Annemarie E. Fogerty, MD[8]; Shuwei Gao, MD[9]; Samuel Z. Goldhaber, MD[6]; Krishna Gundabolu, MD[10]; Ibrahim Ibrahim, MD[11]; Eric Kraut, MD[12]; Andrew D. Leavitt, MD[13]; Alfred Lee, MD, PhD[14]; Jason T. Lee, MD[15]; Ming Lim, MD[16]; Janelle Mann, PharmD[17]; Karlyn Martin, MD[18]; Brandon McMahon, MD[19]; John Moriarty, MD[20]; Colleen Morton, MD[21]; Thomas L. Ortel, MD, PhD[22]; Rita Paschal, MD[23]; Jordan Schaefer, MD[24]; Sanford Shattil, MD[25]; Tanya Siddiqi, MD[26]; Deepak Sudheendra, MD, RVPI[27]; Eliot Williams, MD[28]; Liz Hollinger, BSN, RN[29]; and Mai Q. Nguyen, PhD[29]

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.

J Natl Compr Canc Netw 2021;19(10):1181–1201
doi: 10.6004/jnccn.2021.0047

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [2]Moffitt Cancer Center; [3]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [4]Mayo Clinic Cancer Center; [5]Roswell Park Comprehensive Cancer Center; [6]Dana-Farber/Brigham and Women's Cancer Center; [7]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [8]Massachusetts General Hospital Cancer Center; [9]The University of Texas MD Anderson Cancer Center; [10]Fred & Pamela Buffett Cancer Center; [11]UT Southwestern Simmons Comprehensive Cancer Center; [12]Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [13]UCSF Helen Diller Family Comprehensive Cancer Center; [14]Yale Cancer Center/Smilow Cancer Hospital; [15]Stanford Cancer Institute; [16]Huntsman Cancer Institute at the University of Utah; [17]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [18]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [19]University of Colorado Cancer Center; [20]UCLA Jonsson Comprehensive Cancer Center; [21]Vanderbilt-Ingram Cancer Center; [22]Duke Cancer Institute; [23]O'Neal Comprehensive Cancer Center at UAB; [24]University of Michigan Rogel Cancer Center; [25]UC San Diego Moores Cancer Center; [26]City of Hope National Medical Center; [27]Abramson Cancer Center at the University of Pennsylvania; [28]University of Wisconsin Carbone Cancer Center; and [29]National Comprehensive Cancer Network

*Discussion Writing Committee Member.

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.

PLEASE NOTE

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

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.

© National Comprehensive Cancer Network, Inc. 2021. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN.

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.[1] Results from a recent population-based cohort study showed that the presence of cancer increased the risk for VTE by 9-fold.[2] 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.[3] Chemotherapy, antiangiogenic therapy, protein kinase inhibitors and immunotherapy have all been shown to increase the risk of VTE.[2] More importantly, thrombosis is the leading cause of death in cancer patients, second only to cancer itself.[4] Multiple studies have reported significantly higher mortality and reduced overall survival among cancer patients who developed VTE compared with those who did not.[5–10] Specifically, the occurrence of VTE has been reported to increase the likelihood of death for cancer patients by 2- to 6-fold.[8–12] VTE has been reported to be the most common cause of death at 30-day follow-up among cancer patients undergoing surgery.[13] 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.[1,3,5,14,15] Therefore, appropriate use of VTE prophylaxis can bring about substantial benefits in patients at-risk.[16,17] 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.[18–22] There are many treatment options for VTE, encompassing anticoagulants, thrombolytics, mechanical devices and surgical procedures, with their own pros and cons.[16,23] 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.[6,13] In addition, obesity has been identified as a risk factor for VTE.[24–27] Other modifiable risk factors for VTE are

Table 1. VTE Risk Factors in Patients With Cancer

Patient-Related Risk Factors • Older age • Obesity (modifiable) • Smoking, tobacco use (modifiable) • Activity level/exercise (modifiable) • Familial and/or acquired hypercoagulability (including pregnancy) • Medical comorbidities: infection, renal disease, pulmonary disease, congestive heart failure, arterial thromboembolism • Prior VTE • Hospitalization, prolonged immobilization • Poor performance status	**Treatment-Related Risk Factors** • Major surgery • Central venous catheter/intravenous catheter • Chemotherapy • Protein kinase inhibitors • Immunotherapy • Exogenous hormonal therapies • Antiangiogenic agents
Cancer-Related 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	**Risk Assessment in Cancer Outpatients**[26] • Active cancers associated with high incidence of VTE: ◦ Very high risk (stomach, pancreas) ◦ High risk (lung, lymphoma, gynecologic, bladder, testicular) • Prechemotherapy platelet count ≥350 × 10^9/L • Hemoglobin level <10 g/dL or use of red cell growth factors • Prechemotherapy WBC count ≥11 × 10^9/L • Body mass index ≥35 kg/m^2

Abbreviation: VTE, venous thromboembolism.

smoking/tobacco use and level of physical activity.[28–33] There might be confounding factors such as other smoking-attributable diseases and higher BMI in the association between smoking and VTE.[29,30] 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.[28,32,33]

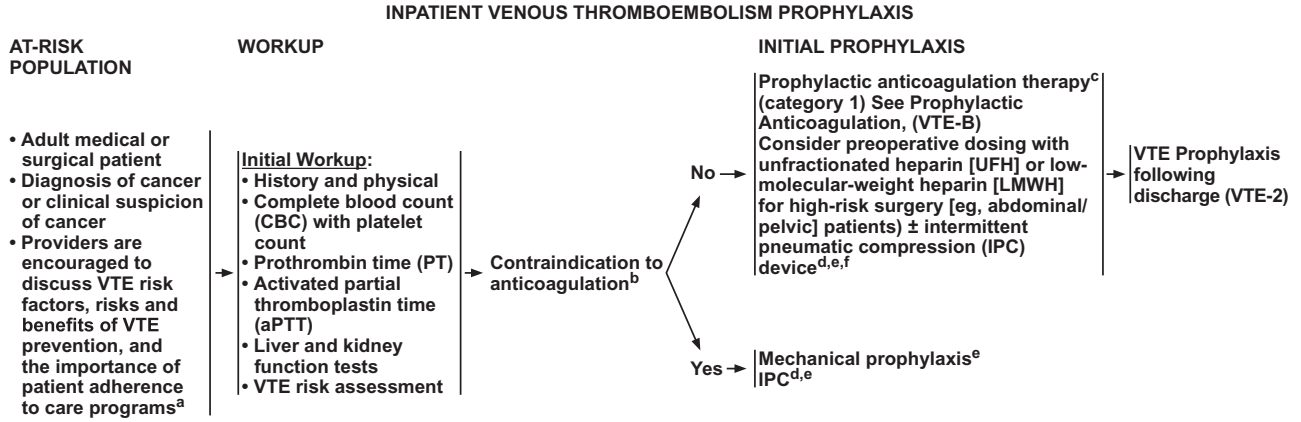
A number of other patient-related VTE risk factors, although not exclusive to patients with cancer, are commonly found. These risk factors include familial and/or acquired hypercoagulability[34,35] (eg strong thrombophilia such as antiphospholipid syndrome,[36,37] pregnancy[38–40]) and other medical comorbidities, such as infection.[41,42] Although factor V Leiden and prothrombin gene 20210 mutations were identified in 3.7% and 2.6%, respectively, of patients with breast or colon cancer receiving adjuvant chemotherapy, these inherited risk factors were not associated with an increased risk for VTE among patients with cancer.[43]

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.[42] Other noteworthy independent risk factors for VTE development include renal disease,[44–46] pulmonary disease,[47–50] congestive heart failure,[51,52] and arterial thromboembolism.[53–55] A history of prior VTE has also been identified as an independent risk factor for developing a subsequent VTE.[13,43,56–58] 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.[59]

Other patient-related characteristics that are considered major risk factors for VTE development include hospitalization, prolonged immobilization, and poor performance status.[60–62] 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.[63] 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.[60] Additionally, several studies have evaluated the association between types of cancer and the risk for developing VTE.[1,3,6,8,64–66] Pancreatic cancer[3,6,8,64–67] and brain tumors[6,66,68] 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.[69,70] Although differences in study designs make it difficult to compare VTE rates according to a specific type of malignancy,



[a] The NCCN Guidelines Panel for Cancer-Associated Venous Thromboembolic Disease recommends VTE prophylaxis for all hospitalized cancer patients. Although multiple risk assessment models (RAMs) have been developed for hospitalized medical and surgical patients, none of these RAMs have been validated in prospective management studies conducted in hospitalized cancer patients.
[b] See Contraindications to VTE Prophylaxis (VTE-A).
[c] Discuss VTE prevention and the risks/benefits of pharmacologic and mechanical VTE prophylaxis. 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.
[d] In contrast to graduated compression stockings (GCS), IPC significantly reduced deep vein thrombosis (DVT) and was associated with a lower risk of skin complications. (Dennis M, et al. Lancet 2013;382:516-524; and CLOTS Trials Collaboration, et al. Lancet 2009;373:1958-1965.)
[e] Most data come from surgical or stroke patients; this is an extrapolation to the medical population. See Contraindications to Mechanical VTE Prophylaxis (VTE-A).
[f] 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. (Arabi YM, et al. N Engl J Med 2019;380:1305-1315.)

VTE-1

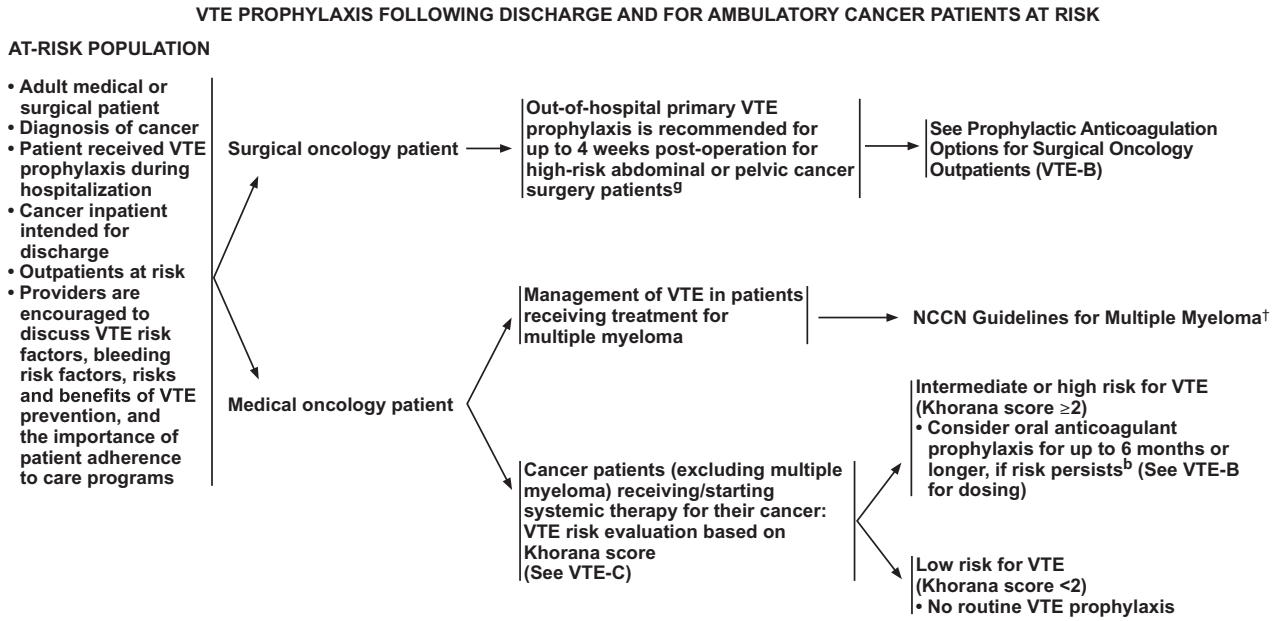
other cancers that have been associated with an increased risk for VTE include cancers of the stomach, kidney, uterus, lung, ovary, bladder, and testis.[1,3,6] In contrast, breast cancer was associated with a relatively low VTE risk in some studies.[9,71] Nevertheless, due to the relatively high prevalence of breast cancer, VTE in patients with breast cancer is not uncommon.[9,71]

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).[6,72] 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.[73,74] 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.[75] 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.[1,66,67,76–78] 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.[1] 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.[78]

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.[60] 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%).[79] Importantly, a significant proportion of VTE episodes (34%) among surgical oncology



[†]To view the most recent version of these guidelines, visit NCCN.org.

[b] See Contraindications to VTE Prophylaxis (VTE-A).
[g] High-risk abdominal/pelvic cancer surgery patients include patients undergoing surgery for gastrointestinal malignancies, patients with a previous history of VTE, anesthesia time >2 hours, bed rest ≥4 days, advanced-stage disease, and patient age >60 years.

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 CVAD[86,87] 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/dL[26,90] 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.[98] Use of hormonal compounds, such as hormone replacement therapy[98,99] 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[1]

Contraindications to Prophylactic Anticoagulation

- Active bleeding
- Thrombocytopenia (platelet count <50,000/μL or clinical judgment)[2]
- 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[3,4]
- Interventional spine and pain procedures[5]

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[6]
  - Mild arterial insufficiency (pertains to GCS only)
  - Peripheral neuropathy (pertains to GCS only)

*Available online, in these guidelines, at NCCN.org.

[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.
[5] Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med 2015;40:182-212.
[6] Skin ulcerations and wounds are more common with the use of GCS.

VTE-A

contraceptives do not definitively increase the risk of VTE in the general population, but may contribute to VTE risk in patients with multiple risk factors.[105]

Finally, the association between immunomodulating agents with antiangiogenic properties (eg thalidomide in combination with doxorubicin and/or dexamethasone; lenalidomide in combination with dexamethasone) and increased incidence of VTE has been supported by multiple studies, most often in the context of treatment for 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).[106–108] ESAs, which are used to treat anemia in patients with cancer, have also been associated with the development of VTE, and though they remain a reasonable option for supportive care, attention to the safety and risks/benefits must be considered.[3,90,109,110]

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 ($\geq 350 \times 10^9$/L), decreased hemoglobin level (<10 g/dL) or use of ESAs, increased prechemotherapy leukocyte count ($>11 \times 10^9$/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

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

Agent	Standard Dosing[a,b]	Renal Dose	Obesity Dosing (BMI ≥40 kg/m^2)[c]
Dalteparin[1,2,3,4]	5,000 units SC daily (category 1)	Avoid if CrCl <30 mL/min	Consider 7,500 units SC daily OR 5,000 units SC every 12 hours OR 40–75 units/kg SC daily
Enoxaparin[3,4,5,6]	40 mg SC daily (category 1)	Recommend 30 mg SC daily if CrCl <30 mL/min	Consider 40 mg SC every 12 hours OR 0.5 mg/kg SC daily
Fondaparinux[4,7,8,10]	2.5 mg SC daily (category 1) Avoid in patients weighing <50 kg	Caution if CrCl 30–49 mL/min Avoid if CrCl <30 mL/min	Consider 5 mg SC daily
Unfractionated Heparin[9,10] (UFH)	5,000 units SC every 8–12 hours (category 1)	Same as standard dose	Consider 7,500 units SC every 8 hours

CrCl = estimated creatinine clearance; SC = subcutaneous

[a] Recommendations derived from patients hospitalized with medical illness (hospitalized >6 days, immobile/bed rest >3 days, age ≥40 years, plus additional risk factors for VTE).
[b] Thromboprophylaxis for duration of hospital stay or 6–14 days or until patient is fully ambulatory.
[c] Limited to no data available to support recommendations. Recommended doses are derived from non-oncology populations.

VTE-B
1 OF 5

patient populations and follow-up periods.[111–115] 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.[26] 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.[112] 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,[111] 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,[116] several other risk assessment models have been published including the Protecht model,[117] the CONKO score,[118] the ONKOTEV score,[119] the TicOnco score,[120] and the COMPASS CAT model.[121] 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 – 0.57).[122] 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.[123,124]

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.[125–129] 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.[130] Similar results were documented in the multinational IMPROVE and ENDORSE registries of hospitalized medically ill patients in which

VTE PROPHYLAXIS OPTIONS FOR AMBULATORY MEDICAL ONCOLOGY PATIENTS (VTE-2)[d,e]

Agent	Standard Dosing[d]	Renal Dose	Other Dose Modifications
Apixaban[f,11]	2.5 mg PO twice daily	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL Avoid if weight <40 kg
Rivaroxaban[g,12]	10 mg PO once daily	Avoid if <15 mL//min	Avoid if platelet count <50,000/μL
Dalteparin[h,13]	200 units/kg SC daily x 1 month, then 150 units/kg SC daily x 2 months	Avoid if CrCl <30 mL/min	Avoid if platelet count <50,000/μL Avoid if weight <40 kg
Enoxaparin[h,14]	1 mg/kg SC daily x 3 months, then 40 mg SC daily	Avoid if CrCl <30 mL/min	Reduce dose to 0.5 mg/kg SC daily for platelet count 50,000-75,000/μL Avoid if platelet count <50,000/μL

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

†To view the most recent version of these guidelines, visit NCCN.org.

[d] Recommendations derived from clinical trials of high thrombosis risk ambulatory cancer patients (>18 years, Khorana VTE Risk Score of ≥2, initiating new course of chemotherapy) and are not included in product labeling. Prophylaxis duration should be 6 months or longer if risk persists.
[e] For recommendations for thromboprophylaxis in multiple myeloma patients, (See NCCN Guidelines for Multiple Myeloma†)
[f] 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.
[g] DOACs are absorbed primarily in the stomach and proximal small bowel, so may not be appropriate for patients who have had significant resections of these portions of the intestinal tracts.
[h] Data support the use of prophylactic dalteparin and enoxaparin for patients with advanced unresectable and metastatic pancreatic cancer (Maraveyas A. Eur J Cancer 2012; Pelzer U. et al. J Clin Oncol 2015.).

only 45% of patients with cancer received any form of VTE prophylaxis.[131,132] 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.[133–136]

Inpatient VTE Prophylaxis

At-Risk Population

Hospitalized patients with cancer are at high risk for VTE.[6] 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,[137–140] 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)

Agent	Standard Dosing[i,j]	Renal Dose	Obesity Dosing (BMI ≥40 kg/m^2)[c]
Dalteparin[1,2,3,4]	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	Avoid if CrCl <30 mL/min	Consider 7,500 units SC daily OR 5,000 units SC every 12 hours OR 40–75 units/kg SC daily
Enoxaparin[3,4,5,6]	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	Recommend 30 mg SC daily if CrCl <30 mL/min	Consider 40 mg SC every 12 hours
Fondaparinux[3,4,6,7,8]	2.5 mg SC daily no earlier than 6–8 hours post-operation Avoid in patients weighing <50 kg	Caution if CrCl 30–49 mL/min Avoid if CrCl <30 mL/min	Consider 5 mg SC daily
UFH[13,14,15]	5,000 units SC 2–4 hours prior to surgery then 5,000 units SC every 8 hours through post-operative day 1	Same as standard dose	Consider 7,500 units SC every 8 hours post-operation
Apixaban[f,k,16]	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	Avoid if CrCl <30 mL/min	No dose adjustment available

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

[c] Limited to no data available to support recommendations. Recommended doses are derived from non-oncology populations.
[f] 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.
[i] Recommendations derived from patients undergoing planned, elective, open abdominal or pelvic surgery for malignancy (OR time >45 minutes, age >40 years).
[j] Thromboprophylaxis for 7–10 days or until patient is fully ambulatory.
[k] Only applies to gynecologic oncology patients. Apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed. Duration of prophylaxis was 28 days.

VTE-B
3 OF 5

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 (dalteparin[141–143] and enoxaparin[144–147]), fondaparinux,[148–150] and UFH[149,151] 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 [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

EXTENDED VTE PROPHYLAXIS OPTIONS FOR SURGICAL ONCOLOGY PATIENTS (VTE-2)

Agent	Standard Dosing[i]	Renal Dose[1,5]
Apixaban[f,k,16]	2.5 mg PO every 12 hours x 28 days	Avoid if CrCl <30 mL/min
Dalteparin[l,14,17,18]	5,000 units SC daily x 28 days	Avoid if CrCl <30 mL/min
Enoxaparin[l,15,17,19,20]	40 mg SC daily x 28 days	Avoid if CrCl <30 mL/min

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

[f] 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.
[i] Recommendations derived from patients undergoing planned, elective, open abdominal and pelvic surgery for malignancy (OR time >45 minutes, age ≥40 years)
[k] Only applies to gynecologic oncology patients. Apixaban was initiated at investigator discretion once epidural anesthesia catheters were removed. Duration of prophylaxis was 28 days.
[l] 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]

VTE-B 4 OF 5

determined to significantly lower the frequency of DVT in the legs (26% vs 4% with placebo; $P<.01$).[151] 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] enoxaparin[144,158]), fondaparinux,[129,148,159] UFH,[160–163] and apixaban[164] (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 Thombocytopenia," 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]

VTE PROPHYLAXIS OPTIONS FOR HOSPITALIZED PATIENTS
REFERENCES

[1] Prescribing information: Dalteparin sodium injection, for subcutaneous use; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020287Orig1s076lbl.pdf.
[2] Kucher N, Leizorovicz A, Vaitkus PT, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005;165:341-345.
[3] Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: Available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009;43:1064-1083.
[4] Freeman AL, Pendelton RC, Rondina MT. Prevention of VTE in obesity. Expert Rev Cardiovasc Ther 2010;8:1711-1721.
[5] Prescribing information: Enoxaparin sodium injection, for subcutaneous use; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020164s116lbl.pdf
[6] Abildgaard A, Madsen S, Hvas AM. Dosage of anticoagulants in obesity: Recommendations based on a systemic review. Semin Thromb Hemost 2020;46:932-969.
[7] Prescribing information: Fondaparinux sodium solution for subcutaneous injection; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021345Orig1s043lbl.pdf.
[8] Martinez L, Burnett A, Borrego M, et al. Effect of fondaparinux prophylaxis on anti-factor Xa concentrations in patients with morbid obesity. Am J Health Syst Pharm. 2011;68:1716-1722. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021345Orig1s043lbl.pdf.
[9] Dentali F, Douketis JD, Gianni M, et al. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007;146:278-288.
[10] Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Practice Guidelines Chest Physicians Evidence-Based Clinical Thrombosis, 9th ed. Chest 2012;141;e195S-e226S.
[11] Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent VTE in patients with cancer. N Engl J Med 2019;380:711-719.
[12] Khorana AA, Kakkar AK, Vadhan-Raj H, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019;380:720-728.
[13] Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012;48:1283-1292.
[14] Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: Outcomes from the CONKO-004 Trial. J Clin Oncol 2015;33:2028-2034.
[15] Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 1988;318:1162-1173.
[16] Guntupalli SR, Brennecke A, Behbakht K, et al. Safety and efficacy of apixaban vs enoxaparin for preventing postoperative venous thromboembolism in women undergoing surgery for gynecologic malignant neoplasm: A randomized clinical trial. JAMA Netw Open 2020;3:e207410.
[17] Gould MA, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S-277S.
[18] Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost 2006;4:2384-2390.
[19] Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2019;8:CD004318.
[20] Bergqvist D, Agnelli GC, Cohen AT, et al. Duration of prophylaxis against VTE with enoxaparin after surgery for cancer. N Engl J Med 2002;346:975-980.

VTE-B
5 OF 5

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.[168] 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.[169] 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.[170,171] In contrast to enoxaparin, dalteparin might not accumulate in patients with severe renal function.[172,173] LMWH accumulation can increase the risk of major bleeding; thus, its benefits must be carefully weighed against potential complications in this subset of patients.[174]

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.[174] 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.[175–178] 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.[68] If enoxaparin is used, it should be dosed at 30 mg subcutaneously once daily.[168] In those with moderate renal disease (CrCl, 30-49 mL/min), fondaparinux should be used with caution.[148,149]

Obesity Dosing

It has been suggested that fixed doses of anticoagulants might not be sufficient in obese patients.[179–181] 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.[182,183] Although there are limited data available to support dosing recommendations for patients with cancer with BMI $\geq$40kg/m^2, the NCCN panel suggests consideration of increased prophylactic anticoagulation doses in obese hospitalized medical and surgical oncology patients.

VTE RISK ASSESSMENT IN CANCER OUTPATIENTS

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 or higher	1
• Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
• Prechemotherapy leukocyte count higher than 11 x 10^9/L	1
• BMI 35 kg/m^2 or higher	1

Total Score	Risk Category	Risk of Symptomatic VTE[2]
0	Low	0.3–1.5%
1, 2	Intermediate	2.0–4.8%
3 or higher	High	6.7–12.9%

[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.
[2] Khorana AA. Cancer and Coagulation. Am J Hematol 2012;87 Supp 1:S82-87.

VTE-C

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,[184] 5,000 units every 12 hours,[185] or 40 – 75 units/kg daily[186]), enoxaparin (40 mg every 12 hours[179–181,187–194] or 0.5 mg/kg daily[195–197]), fondaparinux (5 mg daily[198]), and UFH (7,500 units every 8 hours[191]). Prospective invest-igations 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.[199–201] 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.[199] Additionally, in contrast to graduated compression stockings (GCS), IPC significantly reduced DVT and was associated with a lower risk of skin complications.[201,202] 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%).[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.[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.[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

decade ago and used fibrinogen uptake scans as a primary outcome measure—a now antiquated diagnostic method.[206] 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.[207] 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.[202] 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.[208] 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.[209] 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.[13] 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.

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,[124] rivaroxaban[123]) and LMWHs (dalteparin[210] and enoxaparin[211]) 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.[123,124] 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; $P<.001$).[124] 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; $P=.10$).[123] 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% ($P=.002$).[210] 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; $P=.01$).[211]

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

1186). 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.[13,203] 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.[13] Extended anticoagulant options for surgical oncology patients are listed in the algorithm (see VTE-B 4 of 5, page 1190). Apixaban[165] and LMWHs (dalteparin[157,211,212] and enoxaparin[168,164,212]) 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.[167] 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.[157,158] 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).[157] 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).[158] 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).[213]

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,[124] rivaroxaban, which is only recommended for ambulatory medical oncology patients, should be avoided for CrCl <15 mL/min.[214]

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.[141,144,148] UFH should also be used with extreme caution in patients receiving spinal anesthesia or undergoing spinal puncture.[215] Anticoagulant prophylaxis is usually considered unsafe for platelet count less than 50,000/μL.[216] 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.[217–219]

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.[220,221] Any patient who has experienced a thrombotic event and fulfills diagnostic criteria for antiphospholipid syndrome should be considered for indefinite anticoagulation therapy.[221]

Contraindications to Mechanical Anticoagulation

Whenever mechanical prophylaxis is used, steps should be taken to ensure its proper use and continuous application. (see VTE-A, page 1186). 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.[201,202] 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.[222]

Summary

In the 2021 update, the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease was 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 noncancer 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.

References

1. Blom JW, Doggen CJM, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715–722. https://doi.org/10.1001/jama.293.6.715
2. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood 2021;137:1959–1969.
3. Khorana AA, Dalal M, Lin J, et al. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer 2013;119:648–655.
4. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5:632–634.
5. Khorana AA, Francis CW, Culakova E, et al. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007;110:2339–2346.
6. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol 2006;24:484–490.
7. Fotopoulou C, duBois A, Karavas AN, et al. Incidence of venous thromboembolism in patients with ovarian cancer undergoing platinum/paclitaxel-containing first-line chemotherapy: an exploratory analysis by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. J Clin Oncol 2008;26:2683–2689.
8. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006;166:458–464.
9. Chew HK, Wun T, Harvey DJ, et al. Incidence of venous thromboembolism and the impact on survival in breast cancer patients. J Clin Oncol 2007;25:70–76.
10. Sørensen HT, Mellemkjaer L, Olsen JH, et al. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343:1846–1850.
11. Kuderer NM, Francis CW, Culakova E, et al. Venous thromboembolism and all-cause mortality in cancer patients receiving chemotherapy (abstract). J Clin Oncol 2008;26(Supple 15):Abstract 9521.
12. Martino MA, Williamson E, Siegfried S, et al. Diagnosing pulmonary embolism: experience with spiral CT pulmonary angiography in gynecologic oncology. Gynecol Oncol 2005;98:289–293.
13. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 2006;243:89–95.
14. Ohashi Y, Ikeda M, Kunitoh H, et al. Venous thromboembolism in cancer patients: report of baseline data from the multicentre, prospective Cancer-VTE Registry. Jpn J Clin Oncol 2020;50:1246–1253.
15. Rickles FR, Levine MN. Epidemiology of thrombosis in cancer. Acta Haematol 2001;106:6–12.
16. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2020;38:496–520.
17. Farge D, Bounameaux H, Brenner B, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2016;17:e452–e466.
18. Heit JA, Silverstein MD, Mohr DN, et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 1999;159:445–453.
19. Aggarwal A, Fullam L, Brownstein AP, et al. Deep vein thrombosis (DVT) and pulmonary embolism (PE): awareness and prophylaxis practices reported by patients with cancer. Cancer Invest 2015;33:405–410.
20. Secin FP, Jiborn T, Bjartell AS, et al. Multi-institutional study of symptomatic deep venous thrombosis and pulmonary embolism in prostate cancer patients undergoing laparoscopic or robot-assisted laparoscopic radical prostatectomy. Eur Urol 2008;53:134–145.
21. Girard P, Decousus M, Laporte S, et al. Diagnosis of pulmonary embolism in patients with proximal deep vein thrombosis: specificity of symptoms and perfusion defects at baseline and during anticoagulant therapy. Am J Respir Crit Care Med 2001;164:1033–1037.
22. Anderson FA, Jr., Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991;151:933–938.
23. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. JAMA 2014;311:717–728.
24. Ageno W, Squizzato A, Garcia D, et al. Epidemiology and risk factors of venous thromboembolism. Semin Thromb Hemost 2006;32:651–658.
25. Connolly GC, Khorana AA. Emerging risk stratification approaches to cancer-associated thrombosis: risk factors, biomarkers and a risk score. Thromb Res 2010;125(Suppl 2):S1–S7.
26. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902–4907.
27. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med 2005;118:978–980.
28. Borch KH, Hansen-Krone I, Braekkan SK, et al. Physical activity and risk of venous thromboembolism: the Tromso study. Haematologica 2010;95:2088–2094.
29. Cheng YJ, Liu ZH, Yao FJ, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med 2013;10:e1001515.
30. Enga KF, Braekkan SK, Hansen-Krone IJ, et al. Cigarette smoking and the risk of venous thromboembolism: the Tromsø Study. J Thromb Haemost 2012;10:2068–2074.
31. Hansson PO, Eriksson H, Welin L, et al. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". Arch Intern Med 1999;159:1886–1890.
32. Danin-Mankowitz H, Ugarph-Morawski A, Braunschweig F, et al. The risk of venous thromboembolism and physical activity level, especially high level: a systematic review. J Thromb Thrombolysis 2021.
33. van Stralen KJ, Doggen CJ, Lumley T, et al. The relationship between exercise and risk of venous thrombosis in elderly people. J Am Geriatr Soc 2008;56:517–522.

34. Mahmoodi BK, Brouwer JL, Ten Kate MK, et al. A prospective cohort study on the absolute risks of venous thromboembolism and predictive value of screening asymptomatic relatives of patients with hereditary deficiencies of protein S, protein C or antithrombin. J Thromb Haemost 2010;8:1193–1200.
35. Poort SR, Rosendaal FR, Reitsma PH, et al. A common genetic variation in the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698–3703.
36. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–1027.
37. Ginsburg KS, Liang MH, Newcomer L, et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med 1992;117:997–1002.
38. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv 2018;2:3360–3392.
39. Segal JB, Streiff MB, Hofmann LV, et al. Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med 2007;146:211–222.
40. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance–United States, 1991–1999. MMWR Surveill Summ 2003;52:1–8.
41. Rogers MA, Levine DA, Blumberg N, et al. Triggers of hospitalization for venous thromboembolism. Circulation 2012;125:2092–2099.
42. Schmidt M, Horvath-Puho E, Thomsen RW, et al. Acute infections and venous thromboembolism. J Intern Med 2012;271:608–618.
43. Mandalà M, Barni S, Prins M, 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.
44. Lu HY, Liao KM. Increased risk of deep vein thrombosis in end-stage renal disease patients. BMC Nephrol 2018;19:204.
45. Monreal M, Falgá C, Valle R, et al. Venous thromboembolism in patients with renal insufficiency: findings from the RIETE Registry. Am J Med 2006;119:1073–1079.
46. Wattanakit K, Cushman M, Stehman-Breen C, et al. Chronic kidney disease increases risk for venous thromboembolism. J Am Soc Nephrol 2008;19:135–140.
47. Børvik T, Brækkan SK, Enga K, et al. COPD and risk of venous thromboembolism and mortality in a general population. Eur Respir J 2016;47:473–481.
48. Kim V, Goel N, Gangar J, et al. Risk factors for venous thromboembolism in chronic obstructive pulmonary disease. Chronic Obstr Pulm Dis (Miami) 2014;1:239–249.
49. Piazza G, Goldhaber SZ, Kroll A, et al. Venous thromboembolism in patients with chronic obstructive pulmonary disease. Am J Med 2012;125:1010–1018.
50. Bertoletti L, Quenet S, Laporte S, et al. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: data from the RIETE registry. Respir Res 2013;14:75.
51. Tang L, Wu YY, Lip GY, et al. Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis. Lancet Haematol 2016;3:e30–e44.
52. Leizorovicz A, Turpie AG, Cohen AT, et al. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART study. J Thromb Haemost 2005;3:28–34.
53. Eliasson A, Bergqvist D, Björck M, et al. Incidence and risk of venous thromboembolism in patients with verified arterial thrombosis: a population study based on 23,796 consecutive autopsies. J Thromb Haemost 2006;4:1897–1902.
54. Hong C, Zhu F, Du D, et al. Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism. Atherosclerosis 2005;183:169–174.
55. Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med 2003;348:1435–1441.
56. Darze ES, Latado AL, Guimarães AG, et al. Incidence and clinical predictors of pulmonary embolism in severe heart failure patients admitted to a coronary care unit. Chest 2005;128:2576–2580.
57. Kröger K, Weiland D, Ose C, et al. Risk factors for venous thromboembolic events in cancer patients. Ann Oncol 2006;17:297–303.
58. Prandoni P, Lensing AWA, Prins MH, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 2002;137:955–960.
59. Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484–3488.
60. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med 2002;162:1245–1248.
61. Beam DM, Courtney DM, Kabrhel C, et al. Risk of thromboembolism varies, depending on category of immobility in outpatients. Ann Emerg Med 2009;54:147–152.
62. Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, et al. Body height, mobility, and risk of first and recurrent venous thrombosis. J Thromb Haemost 2015;13:548–554.
63. Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations - United States, 2007-2009. MMWR Morb Mortal Wkly Rep 2012;61:401–404.
64. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore) 1999;78:285–291.
65. Ogren M, Bergqvist D, Wåhlander K, et al. Trousseau's syndrome - what is the evidence? A population-based autopsy study. Thromb Haemost 2006;95:541–545.
66. Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. Thromb Haemost 2002;87:575–579.
67. Hall IE, Andersen MS, Krumholz HM, et al. Predictors of venous thromboembolism in patients with advanced common solid cancers. J Cancer Epidemiol 2009;2009:182521–182521.
68. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. Cancer 2000;89:640–646.
69. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. J Thromb Haemost 2008;6:1983–1985.
70. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. Clin Cancer Res 2007;13:2870–2875.
71. Andtbacka RHI, Babiera G, Singletary SE, et al. Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. Ann Surg 2006;243:96–101.
72. Carrier M, Le Gal G, Tay J, et al. Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: a systematic review and meta-analysis. J Thromb Haemost 2011;9:653–663.
73. De Stefano V, Sorà F, Rossi E, et al. The risk of thrombosis in patients with acute leukemia: occurrence of thrombosis at diagnosis and during treatment. J Thromb Haemost 2005;3:1985–1992.
74. Mohren M, Markmann I, Jentsch-Ullrich K, et al. Increased risk of thromboembolism in patients with malignant lymphoma: a single-centre analysis. Br J Cancer 2005;92:1349–1351.
75. Ottinger H, Belka C, Kozole G, et al. Deep venous thrombosis and pulmonary artery embolism in high-grade non Hodgkin's lymphoma: incidence, causes and prognostic relevance. Eur J Haematol 1995;54:186–194.
76. Hicks LK, Cheung MC, Ding K, et al. Venous thromboembolism and nonsmall cell lung cancer: a pooled analysis of National Cancer Institute of Canada Clinical Trials Group trials. Cancer 2009;115:5516–5525.
77. Sandhu R, Pan C-X, Wun T, et al. The incidence of venous thromboembolism and its effect on survival among patients with primary bladder cancer. Cancer 2010;116:2596–2603.
78. Gade IL, Braekkan SK, Naess IA, et al. The impact of initial cancer stage on the incidence of venous thromboembolism: the Scandinavian Thrombosis and Cancer (STAC) Cohort. J Thromb Haemost 2017;15:1567–1575.
79. Hammond J, Kozma C, Hart JC, et al. Rates of venous thromboembolism among patients with major surgery for cancer. Ann Surg Oncol 2011;18:3240–3247.
80. Toledano TH, Kondal D, Kahn SR, et al. The occurrence of venous thromboembolism in cancer patients following major surgery. Thromb Res 2013;131:e1–e5.

81. Baarslag HJ, Koopman MMW, Hutten BA, et al. Long-term follow-up of patients with suspected deep vein thrombosis of the upper extremity: survival, risk factors and post-thrombotic syndrome. Eur J Intern Med 2004;15:503–507.
82. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000;160:809–815.
83. Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med 1997;157:57–62.
84. Lee AY, Levine MN, Butler G, et al. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. J Clin Oncol 2006;24:1404–1408.
85. Gerber DE, Segal JB, Levy MY, et al. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. Blood 2008;112:504–510.
86. Joffe HV, Goldhaber SZ. Upper-extremity deep vein thrombosis. Circulation 2002;106:1874–1880.
87. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol 2003;21:3665–3675.
88. van Rooden CJ, Schippers EF, Barge RMY, et al. Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. J Clin Oncol 2005;23:2655–2660.
89. Lordick F, Hentrich M, Decker T, et al. Ultrasound screening for internal jugular vein thrombosis aids the detection of central venous catheter-related infections in patients with haemato-oncological diseases: a prospective observational study. Br J Haematol 2003;120:1073–1078.
90. Khorana AA, Francis CW, Culakova E, et al. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 2005;104:2822–2829.
91. Otten HM, Mathijssen J, ten Cate H, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. Arch Intern Med 2004;164:190–194.
92. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189–2197.
93. Decensi A, Maisonneuve P, Rotmensz N, et al. Effect of tamoxifen on venous thromboembolic events in a breast cancer prevention trial. Circulation 2005;111:650–656.
94. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–1662.
95. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–1388.
96. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. Cancer Prev Res (Phila) 2010;3:696–706.
97. Leaf AN, Propert K, Corcoran C, et al. Phase III study of combined chemohormonal therapy in metastatic prostate cancer (ECOG 3882): an Eastern Cooperative Oncology Group study. Med Oncol 2003;20:137–146.
98. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–1712.
99. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333.
100. Blanco-Molina A, Trujillo-Santos J, Tirado R, et al. Venous thromboembolism in women using hormonal contraceptives. Findings from the RIETE Registry. Thromb Haemost 2009;101:478–482.
101. Lidegaard Ø, Nielsen LH, Skovlund CW, et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343(oct25 4):d6423.
102. Manzoli L, De Vito C, Marzuillo C, et al. Oral contraceptives and venous thromboembolism: a systematic review and meta-analysis. Drug Saf 2012;35:191–205.
103. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ 2011;342(apr21 2):d2151.
104. Parkin L, Sharples K, Hernandez RK, et al. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ 2011;342(apr21 2):d2139.
105. Tepper NK, Dragoman MV, Gaffield ME, et al. Nonoral combined hormonal contraceptives and thromboembolism: a systematic review. Contraception 2017;95:130–139.
106. El Accaoui RN, Shamseddeen WA, Taher AT. Thalidomide and thrombosis: a meta-analysis. Thromb Haemost 2007;97:1031–1036.
107. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133–2142.
108. Zangari M, Siegel E, Barlogie B, et al. Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy. Blood 2002;100:1168–1171.
109. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299:914–924.
110. Connolly GC, Dalal M, Lin J, et al. Incidence and predictors of venous thromboembolism (VTE) among ambulatory patients with lung cancer. Lung Cancer 2012;78:253–258.
111. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. Blood 2010;116:5377–5382.
112. Mandala M, Clerici M, Corradino I, et al. Incidence, risk factors and clinical implications of venous thromboembolism in cancer patients treated within the context of phase I studies: the 'SENDO experience'. Ann Oncol 2012;23:1416–1421.
113. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 2011;29:3466–3473.
114. Kearney JC, Rossi S, Glinert K, et al. Venous thromboembolism (VTE) and survival in a cancer chemotherapy outpatient clinic: a retrospective chart review validation of a VTE predictive model. [abstract] Blood 2009;114:114. (Abstract 2503)
115. Price LH, Nguyen MB, Picozzi VJ, et al. Portal vein thrombosis in pancreatic cancer: Natural history, risk factors, and implications for patient management [abstract]. Proceedings of the Gastrointestinal Cancers Symposium 2010:Abstract 143.
116. Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. Lancet Haematol 2018;5:e289–e298.
117. Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med 2012;7:291–292.
118. Pelzer U, Sinn M, Stieler J, et al. [Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy?]. Dtsch Med Wochenschr 2013;138:2084–2088.
119. Cella CA, Di Minno G, Carlomagno C, et al. Preventing venous thromboembolism in ambulatory cancer patients: the ONKOTEV Study. Oncologist 2017;22:601–608.
120. Muñoz Martín AJ, Ortega I, Font C, et al. Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. Br J Cancer 2018;118:1056–1061.
121. Gerotziafas GT, Taher A, Abdel-Razeq H, et al. A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the Prospective COMPASS-Cancer-Associated Thrombosis study. Oncologist 2017;22:1222–1231.
122. van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica 2017;102:1494–1501.
123. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019;380:720–728.

124. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019;380:711–719.
125. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:381S-453S.
126. Kahn SR, Morrison DR, Diendéré G, et al. Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism. Cochrane Database Syst Rev 2018;4:CD008201.
127. Kakkar VV, Corrigan TP, Fossard DP, et al. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Reappraisal of results of international multicentre trial. Lancet 1977;1:567–569.
128. Mismetti P, Laporte S, Darmon JY, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001;88:913–930.
129. Agnelli G, Bergqvist D, Cohen AT, et al. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg 2005;92:1212–1220.
130. Kakkar AK, Levine M, Pinedo HM, et al. Venous thrombosis in cancer patients: insights from the FRONTLINE survey. Oncologist 2003;8:381–388.
131. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371:387–394.
132. Tapson VF, Decousus H, Pini M, et al. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. Chest 2007;132:936–945.
133. Couban S, Goodyear M, Burnell M, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol 2005;23:4063–4069.
134. Karthaus M, Kretzschmar A, Kröning H, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol 2006;17:289–296.
135. Verso M, Agnelli G, Bertoglio S, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. J Clin Oncol 2005;23:4057–4062.
136. Young AM, Billingham LJ, Begum G, et al. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. Lancet 2009;373:567–574.
137. Spyropoulos AC, Anderson FA, Jr., FitzGerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 2011;140:706–714.
138. Grant PJ, Greene MT, Chopra V, et al. Assessing the Caprini score for risk assessment of venous thromboembolism in hospitalized medical patients. Am J Med 2016;129:528–535.
139. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 2010;8:2450–2457.
140. Greene MT, Spyropoulos AC, Chopra V, et al. Validation of risk assessment models of venous thromboembolism in hospitalized medical patients. Am J Med 2016;129:1001.e1009−1001.e1018.
141. Prescribing information. Dalteparin sodium injection, for subcutaneous use; 2020. Available at: .
142. Kucher N, Leizorovicz A, Vaitkus PT, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005;165:341–345.
143. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874–879.
144. Prescribing information. Enoxaparin sodium injection, for subcutaneous use; 2018. Available at: .
145. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999;341:793–800.
146. Lederle FA, Sacks JM, Fiore L, et al. The prophylaxis of medical patients for thromboembolism pilot study. Am J Med 2006;119:54–59.
147. Kakkar AK, Cimminiello C, Goldhaber SZ, et al. Low-molecular-weight heparin and mortality in acutely ill medical patients. N Engl J Med 2011;365:2463–2472.
148. Prescribing information. Fondaparinux sodium solution for subcutaneous injection; 2020. Available at: .
149. 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.
150. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332:325–329.
151. Belch JJ, Lowe GD, Ward AG, et al. Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J 1981;26:115–117.
152. Dentali F, Douketis JD, Gianni M, et al. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007;146:278–288.
153. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 1988;208:227–240.
154. King CS, Holley AB, Jackson JL, et al. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A metaanalysis. Chest 2007;131:507–516.
155. Prevention of fatal postoperative pulmonary embolism by low doses of heparin: an international multicentre trial. Lancet 1975;2:45–51.
156. Gruber UF, Duckert F, Fridrich R, et al. Prevention of postoperative thromboembolism by dextran 40, low doses of heparin, or xantinol nicotinate. Lancet 1977;1:207–210.
157. Rasmussen MS, Jorgensen LN, Wille-Jørgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. J Thromb Haemost 2006;4:2384–2390.
158. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002;346:975–980.
159. Turpie AG, Bauer KA, Caprini JA, et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. J Thromb Haemost 2007;5:1854–1861.
160. Kakkar VV, Boeckl O, Boneu B, et al. Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism: European multicenter trial. World J Surg 1997;21:2–8., discussion 8–9.
161. Koppenhagen K, Adolf J, Matthes M, et al. Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. Thromb Haemost 1992;67:627–630.
162. McLeod RS, Geerts WH, Sniderman KW, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the Canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. Ann Surg 2001;233:438–444.
163. ENOXACAN Study Group. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. Br J Surg 1997;84:1099–1103.
164. Guntupalli SR, Brennecke A, Behbakht K, et al. Safety and efficacy of apixaban vs enoxaparin for preventing postoperative venous thromboembolism in women undergoing surgery for gynecologic malignant neoplasm: a randomized clinical trial. JAMA Netw Open 2020;3:e207410.
165. McGowan KE, Makari J, Diamantouros A, et al. Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program. Blood 2016;127:1954–1959.
166. Akl EA, Terrenato I, Barba M, et al. Low-molecular-weight heparin vs unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. Arch Intern Med 2008;168:1261–1269.
167. DeBernardo RL, Jr., Perkins RB, Littell RD, et al. Low-molecular-weight heparin (dalteparin) in women with gynecologic malignancy. Obstet Gynecol 2005;105:1006–1011.
168. Nutescu EA, Spinler SA, Wittkowsky A, et al. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical

practice recommendations across medical and surgical settings. Ann Pharmacother 2009;43:1064–1083.

169. Becker RC, Spencer FA, Gibson M, et al. Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. Am Heart J 2002;143:753–759.
170. Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. Thromb Res 2005;116:41–50.
171. Chow SL, Zammit K, West K, et al. Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. J Clin Pharmacol 2003;43:586–590.
172. Shprecher AR, Cheng-Lai A, Madsen EM, et al. Peak antifactor xa activity produced by dalteparin treatment in patients with renal impairment compared with controls. Pharmacotherapy 2005;25:817–822.
173. Polkinghorne KR, McMahon LP, Becker GJ. Pharmacokinetic studies of dalteparin (Fragmin), enoxaparin (Clexane), and danaparoid sodium (Orgaran) in stable chronic hemodialysis patients. Am J Kidney Dis 2002;40:990–995.
174. Lim W, Dentali F, Eikelboom JW, et al. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. Ann Intern Med 2006;144:673–684.
175. Spinler SA, Inverso SM, Cohen M, et al. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J 2003;146:33–41.
176. Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al. Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin. Chest 2004;125:856–863.
177. Collet JP, Montalescot G, Agnelli G, et al. Non-ST-segment elevation acute coronary syndrome in patients with renal dysfunction: benefit of low-molecular-weight heparin alone or with glycoprotein IIb/IIIa inhibitors on outcomes. The Global Registry of Acute Coronary Events. Eur Heart J 2005;26:2285–2293.
178. Fox KA, Bassand JP, Mehta SR, et al. Influence of renal function on the efficacy and safety of fondaparinux relative to enoxaparin in non ST-segment elevation acute coronary syndromes. Ann Intern Med 2007;147:304–310.
179. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obes Surg 2002;12:19–24.
180. Borkgren-Okonek MJ, Hart RW, Pantano JE, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis 2008;4:625–631.
181. Simone EP, Madan AK, Tichansky DS, et al. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. Surg Endosc 2008;22:2392–2395.
182. Frederiksen SG, Hedenbro JL, Norgren L. Enoxaparin effect depends on body-weight and current doses may be inadequate in obese patients. Br J Surg 2003;90:547–548.
183. Martinez L, Burnett A, Borrego M, et al. Effect of fondaparinux prophylaxis on anti-factor Xa concentrations in patients with morbid obesity. Am J Health Syst Pharm 2011;68:1716–1722.
184. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease: fragmin in unstable coronary artery disease study (FRIC). Circulation 1997;96:61–68.
185. Gaborit B, Moulin PA, Bege T, et al. Lean body weight is the best scale for venous thromboprophylaxis algorithm in severely obese patients undergoing bariatric surgery. Pharmacol Res 2018;131:211–217.
186. Freeman AL, Pendleton RC, Rondina MT. Prevention of venous thromboembolism in obesity. Expert Rev Cardiovasc Ther 2010;8:1711–1721.
187. Escalante-Tattersfield T, Tucker O, Fajnwaks P, et al. Incidence of deep vein thrombosis in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2008;4:126–130.
188. Kardys CM, Stoner MC, Manwaring ML, et al. Safety and efficacy of intravascular ultrasound-guided inferior vena cava filter in super obese bariatric patients. Surg Obes Relat Dis 2008;4:50–54.
189. Rowan BO, Kuhl DA, Lee MD, et al. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. Obes Surg 2008;18:162–166.
190. Steib A, Degirmenci SE, Junke E, et al. Once versus twice daily injection of enoxaparin for thromboprophylaxis in bariatric surgery: effects on antifactor Xa activity and procoagulant microparticles. A randomized controlled study. Surg Obes Relat Dis 2016;12:613–621.
191. Brunetti L, Wassef A, Sadek R, et al. Anticoagulant activity of enoxaparin and unfractionated heparin for venous thromboembolism prophylaxis in obese patients undergoing sleeve gastrectomy. Surg Obes Relat Dis 2019;15:363–373.
192. Celik F, Huitema AD, Hooijberg JH, et al. Fixed-dose enoxaparin after bariatric surgery: the influence of body weight on peak anti-Xa levels. Obes Surg 2015;25:628–634.
193. Ojo P, Asiyanbola B, Valin E, et al. Post discharge prophylactic anticoagulation in gastric bypass patient-how safe? Obes Surg 2008;18:791–796.
194. Singh K, Podolsky ER, Um S, et al. Evaluating the safety and efficacy of BMI-based preoperative administration of low-molecular-weight heparin in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. Obes Surg 2012;22:47–51.
195. Rondina MT, Wheeler M, Rodgers GM, et al. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res 2010;125:220–223.
196. Al Otaib N, Bootah Z, Al Ammari MA, et al. Assessment of anti-factor Xa activity of enoxaparin for venous thromboembolism prophylaxis in morbidly obese surgical patients. Ann Thorac Med 2017;12:199–203.
197. Freeman A, Horner T, Pendleton RC, et al. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol 2012;87:740–743.
198. Steele KE, Canner J, Prokopowicz G, et al. The EFFORT trial: Preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: a randomized double-blind pilot trial. Surg Obes Relat Dis 2015;11:672–683.
199. Clarke-Pearson DL, Synan IS, Dodge R, et al. A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. Am J Obstet Gynecol 1993;168:1146–1153., discussion 1153–1154.
200. Ramirez JI, Vassiliu P, Gonzalez-Ruiz C, et al. Sequential compression devices as prophylaxis for venous thromboembolism in high-risk colorectal surgery patients: reconsidering American Society of Colorectal Surgeons parameters. Am Surg 2003;69:941–945.
201. Dennis M, Sandercock P, Reid J, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013;382:516–524.
202. Dennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet 2009;373:1958–1965.
203. Martino MA, Borges E, Williamson E, et al. Pulmonary embolism after major abdominal surgery in gynecologic oncology. Obstet Gynecol 2006;107:666–671.
204. Arabi YM, Al-Hameed F, Burns KEA, et al. Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. N Engl J Med 2019;380:1305–1315.
205. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2000; (3):CD001484.
206. Sachdeva A, Dalton M, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2018;11:CD001484.
207. Cohen AT, Skinner JA, Warwick D, et al. The use of graduated compression stockings in association with fondaparinux in surgery of the hip. A multicentre, multinational, randomised, open-label, parallel-group comparative study. J Bone Joint Surg Br 2007;89:887–892.
208. Shalhoub J, Lawton R, Hudson J, et al. Graduated compression stockings as adjuvant to pharmaco-thromboprophylaxis in elective surgical patients (GAPS study): randomised controlled trial. BMJ 2020;369:m1309.
209. Spencer FA, Lessard D, Emery C, et al. Venous thromboembolism in the outpatient setting. Arch Intern Med 2007;167:1471–1475.
210. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012;48:1283–1292.
211. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. J Clin Oncol 2015;33:2028–2034.
212. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of

Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S−277S.

213. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2019;8:CD004318.
214. Prescribing information. Rivaroxaban tablets, for oral use; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022406s028lbl.pdf.
215. Prescribing information. Heparin sodium injection. USP 2020.
216. Napolitano M, Saccullo G, Marietta M, et al. Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus. Blood Transfus 2019;17:171–180.
217. Khanal N, Bociek RG, Chen B, et al. Venous thromboembolism in patients with hematologic malignancy and thrombocytopenia. Am J Hematol 2016;91:E468–E472.
218. Herishanu Y, Misgav M, Kirgner I, et al. Enoxaparin can be used safely in patients with severe thrombocytopenia due to intensive chemotherapy regimens. Leuk Lymphoma 2004;45:1407–1411.
219. Houghton DE, Key NS, Zakai NA, et al. Analysis of anticoagulation strategies for venous thromboembolism during severe thrombocytopenia in patients with hematologic malignancies: a retrospective cohort. Leuk Lymphoma 2017;58:2573–2581.
220. Cervera R, Khamashta MA, Shoenfeld Y, et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2009;68:1428–1432.
221. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. JAMA 2006;295:1050–1057.
222. Palfreyman SJ, Michaels JA. A systematic review of compression hosiery for uncomplicated varicose veins. Phlebology 2009;24(Suppl 1)13–33.

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

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Dana Angelini, MD	None	sanofi-aventis U.S. LLC	None	Hematology/Hematology Oncology
Aneel Ashrani, MD, MS	None	None	None	Hematology/Hematology Oncology
Amro Elshoury, MD	AbbVie, Inc.; Blueprint Medicines Corporation; Boston Biomedical, Inc.; and Kartos Therapeutics, Inc.	Bristol-Myers Squibb Company	None	Hematology/Hematology Oncology
John Fanikos, RPH, MBA[a]	Boehringer Ingelheim GmbH; Heron Therapeutics; PhaseBio Pharmaceuticals, Inc.; and Portola Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc.; Allergan; Boehringer Ingelheim GmbH; Pacira; Pfizer Inc.; and Portola Pharmaceuticals, Inc.	None	Pharmacology/Pharmacy
Kleber Yotsumoto Fertrin, MD, PhD	Agios, Inc., and sanofiaventis U.S. LLC	None	None	Hematology/Hematology Oncology
Annemarie E. Fogerty, MD	None	None	None	Hematology/Hematology Oncology, and Medical Oncology
Shuwei Gao, MD	None	None	None	Internal Medicine
Samuel Z. Goldhaber, MD	Bayer HealthCare; Boehringer Ingelheim GmbH; Boston Scientific Corporation; Bristol-Myers Squibb Company; Daiichi-Sankyo Co.; Janssen Pharmaceutica Products, LP; and Pfizer Inc.	None	None	Cardiology
Krishna Gundabolu, MD[a]	None	Bristol-Myers Squibb Company	None	Hematology/Hematology Oncology
Bjorn Holmstrom, MD	None	None	None	Internal Medicine
Ibrahim Ibrahim, MD	None	None	None	Hematology/Hematology Oncology
Eric Kraut, MD	None	None	None	Hematology/Hematology Oncology
Andrew D. Leavitt, MD	BioMarin Pharmaceutical Inc.; Pfizer Inc.; and Sangamo Therapeutics, Inc.	BioMarin Pharmaceutical Inc.; CSL; Dova Pharmaceuticals; and Merck & Co., Inc.	None	Hematology/Hematology Oncology
Alfred Lee, MD, PhD	None	None	None	Hematology/Hematology Oncology
Jason T. Lee, MD	None	None	None	Surgery/Surgical Oncology, and Cardiology
Ming Lim, MD	None	Argenx; Dova Pharmaceuticals; HEMA Biologics; and Sanofi Genzyme	None	Hematology/Hematology Oncology
Janelle Mann, PharmD	None	None	None	Pharmacology/Pharmacy
Karlyn Martin, MD	Janssen Pharmaceutica Products, LP	Penumbra	None	Hematology/Hematology Oncology
Brandon McMahon, MD	None	None	None	Hematology/Hematology Oncology
John Moriarty, MD	AngioDynamics Inc.; Argon Medical; BD Bard; and Boston Scientific Corporation	None	None	Interventional Radiology
Colleen Morton, MD	None	None	None	Hematology/Hematology Oncology
Thomas L. Ortel, MD, PhD	CDC; Instrumentation Laboratory; NIH; Siemens Medical Solutions Diagnostics; and Stago	Instrumentation Laboratory	None	Hematology/Hematology Oncology
Rita Paschal, MD	None	None	None	Hematology/Hematology Oncology
Jordan Schaefer, MD	None	None	None	Hematology/Hematology Oncology, and Medical Oncology
Sanford Shattil, MD	None	None	None	Hematology/Hematology Oncology
Tanya Siddiqi, MD	BeiGene	AstraZeneca Pharmaceuticals LP; Celgene Corporation; and Juno Therapeutics, Inc.	AstraZeneca Pharmaceuticals LP; Janssen Pharmaceutica Products, LP; Pharmacyclics, Inc.; and ResearchToPractice	Hematology/Hematology Oncology
Michael B. Streiff, MD	NovoNordisk; sanofi-aventis U.S. LLC; and Tremeau Pharmaceuticals, inc.	Dispersol Technologies; Janssen Pharmaceutica Products, LP; and Pfizer Inc.	None	Hematology/Hematology Oncology
Deepak Sudheendra, MD, RPVI	None	Boston Scientific Corporation; Expert Witness; Sirtex Medical; and Vesper Medical, Inc.	Boston Scientific Corporation; Sirtex Medical; and Vesper Medical, Inc.	Interventional Radiology
Eliot Williams, MD	None	None	None	Hematology/Hematology Oncology

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
John Fanikos, RPH, MBA: Hospital Quality Foundation, and North American Thrombosis Forum
Krishna Gundabolu, MD: Geron Corporation