ASCO special article abstract

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

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PURPOSE To provide updated recommendations about prophylaxis and treatment of venous thromboembolism (VTE) in patients with cancer.

METHODS PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) and meta-analyses of RCTs published from August 1, 2014, through December 4, 2018. ASCO convened an Expert Panel to review the evidence and revise previous recommendations as needed.

RESULTS The systematic review included 35 publications on VTE prophylaxis and treatment and 18 publications on VTE risk assessment. Two RCTs of direct oral anticoagulants (DOACs) for the treatment of VTE in patients with cancer reported that edoxaban and rivaroxaban are effective but are linked with a higher risk of bleeding compared with low-molecular-weight heparin (LMWH) in patients with GI and potentially genitourinary cancers. Two additional RCTs reported on DOACs for thromboprophylaxis in ambulatory patients with cancer at increased risk of VTE.

RECOMMENDATIONS Changes to previous recommendations: Clinicians may offer thromboprophylaxis with apixaban, rivaroxaban, or LMWH to selected high-risk outpatients with cancer; rivaroxaban and edoxaban have been added as options for VTE treatment; patients with brain metastases are now addressed in the VTE treatment section; and the recommendation regarding long-term postoperative LMWH has been expanded. Re-affirmed recommendations: Most hospitalized patients with cancer and an acute medical condition require thromboprophylaxis throughout hospitalization. Thromboprophylaxis is not routinely recommended for all outpatients with cancer. Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days. Patients with cancer should be periodically assessed for VTE risk, and oncology professionals should provide patient education about the signs and symptoms of VTE.

Additional information is available at www.asco.org/supportive-care-guidelines.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality among patients with cancer.[1,2] Patients with cancer are significantly more likely to develop VTE than people without cancer[3] and experience higher rates of VTE recurrence and bleeding complications during VTE treatment.[4,5]

Comprehensive management of VTE in patients with cancer includes both the identification of patients who are most likely to benefit from pharmacologic prophylaxis as well as the effective treatment to reduce the risk of VTE recurrence and mortality. ASCO first published a guideline on these topics in 2007,[6] with updates in 2013[7] and 2015.[8] The 2015 update re-affirmed the 2013 recommendations. The current update revises several previous recommendations. Most notably, direct oral anticoagulants (DOACs) have been added as options for VTE prophylaxis and treatment.

GUIDELINE QUESTIONS

This clinical practice guideline addresses six clinical questions:

1. Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?
2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?
3. Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?
4. What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on June 4, 2019 and published at jco.org on August 5, 2019: DOI https://doi.org/10.1200/JCO.19.01461

Clinical Practice Guideline Committee approval: May 16, 2019.

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THE BOTTOM LINE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Guideline Question

How should venous thromboembolism (VTE) be prevented and treated in patients with cancer?

Target Population

Adults with cancer.

Target Audience

Oncologists, surgeons, oncology nurses, oncology pharmacists, other health care professionals who care for patients with cancer, patients, and caregivers.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Clinical Question 1. Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

- Recommendation 1.1. Hospitalized patients who have active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- Recommendation 1.2. Hospitalized patients who have active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- Recommendation 1.3. Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem-cell/bone marrow transplantation (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Clinical Question 2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

- Recommendation 2.1. Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer (Type: evidence based; Evidence quality: intermediate to high; Strength of recommendation: strong).
- Recommendation 2.2. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting (Type: evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: moderate).
- Recommendation 2.3. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical Question 3. Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

- Recommendation 3.1. All patients with malignant disease undergoing major surgical intervention should be offered pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) or LMWH unless contraindicated because of active bleeding, or high bleeding risk, or other contraindications (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- Recommendation 3.2. Prophylaxis should be commenced preoperatively (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- Recommendation 3.3. Mechanical methods may be added to pharmacologic thromboprophylaxis but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because

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THE BOTTOM LINE (CONTINUED)

of active bleeding or high bleeding risk (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.4. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.5. Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 to 10 days. Extended prophylaxis with LMWH for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high-risk features, such as restricted mobility, obesity, history of VTE, or with additional risk factors. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate to strong).

Clinical Question 4. What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

Recommendation 4.1. Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance less than 30 mL/min) (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.2. For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKAs). VKAs are inferior but may be used if LMWH or direct oral anticoagulants (DOACs) are not accessible. There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a DOAC (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.3. Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak to moderate).

Recommendation 4.4. Based on expert opinion in the absence of randomized trial data, uncertain short-term benefit, and mounting evidence of long-term harm from filters, the insertion of a vena cava filter should not be offered to patients with established or chronic thrombosis (VTE diagnosis more than 4 weeks ago), nor to patients with temporary contraindications to anticoagulant therapy (eg, surgery). There also is no role for filter insertion for primary prevention or prophylaxis of pulmonary embolism (PE) or deep vein thrombosis due to its long-term harm concerns. It may be offered to patients with absolute contraindications to anticoagulant therapy in the acute treatment setting (VTE diagnosis within the past 4 weeks) if the thrombus burden was considered life-threatening. Further research is needed (Type: informal consensus; Evidence quality: low to intermediate; Strength of recommendation: moderate).

Recommendation 4.5. The insertion of a vena cava filter may be offered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal anticoagulant therapy. This is based on the panel's expert opinion given the absence of a survival improvement, a limited short-term benefit, but mounting evidence of the long-term increased risk for VTE (Type: informal consensus; Evidence quality: low to intermediate; Strength of recommendation: weak).

Recommendation 4.6. For patients with primary or metastatic CNS malignancies and established VTE, anticoagulation as described for other patients with cancer should be offered, although uncertainties remain about choice of agents and selection of patients most likely to benefit (Type: informal consensus; Quality of evidence: low; Strength of recommendation: moderate).

Recommendation 4.7. Incidental PE and deep vein thrombosis should be treated in the same manner as symptomatic VTE, given their similar clinical outcomes compared with patients with cancer with symptomatic events (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Recommendation 4.8. Treatment of isolated subsegmental PE or splanchnic or visceral vein thrombi diagnosed incidentally should be offered on a case-by-case basis, considering potential benefits and risks of anticoagulation (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Clinical Question 5. Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?

Recommendation 5. Anticoagulant use is not recommended to improve survival in patients with cancer without VTE (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Clinical Question 6. What is known about risk prediction and awareness of VTE among patients with cancer?

Recommendation 6.1. There is substantial variation in risk of VTE between individual patients with cancer and cancer settings. Patients with cancer should be assessed for VTE risk initially and periodically thereafter, particularly when starting systemic antineoplastic therapy or at the time of hospitalization. Individual risk factors, including biomarkers or cancer site, do not reliably identify patients with cancer at high risk of VTE. In the ambulatory setting among patients with solid tumors treated with systemic therapy, risk assessment can be conducted based on a validated risk assessment tool (Khorana score; Table 1) (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.2. Oncologists and members of the oncology team should educate patients regarding VTE, particularly in settings that increase risk, such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Notes regarding off-label use in guideline recommendations: Apixaban, rivaroxaban, and LMWH have not been US Food and Drug Administration–approved for thromboprophylaxis in outpatients with cancer (recommendation 2.2 for apixaban and rivaroxaban; recommendations 2.2 and 2.3 for LMWH). Dalteparin is the only LMWH with US Food and Drug Administration approval for extended therapy to prevent recurrent thrombosis in patients with cancer (recommendation 4.2).

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Additional Resources

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline update.

5. Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?
6. What is known about risk prediction and awareness of VTE among patients with cancer?

METHODS

Guideline Update Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were made available for two open comment periods of 2 weeks each, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. The full guideline was shared with two external reviewers. Comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed using a systematic review and informed by expert clinical experience. For the questions on VTE prophylaxis and treatment, PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) and meta-analyses of RCTs published

between August 1, 2014, and December 4, 2018. Publications were included if they assessed the efficacy and safety of anticoagulation in patients with cancer and included at least 50 patients per arm.

For the question on VTE risk assessment, the search included RCTs, meta-analyses, and cohort studies. Publications were included if they focused on the ambulatory or inpatient setting and assessed validated risk models or developed and validated new risk models.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals, (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews, and (3) published in a non-English language.

The updated search was guided by the "signals"[9] approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help to identify potential signals. Before publication, a review of guideline implementability was also conducted. Ratings for the type and strength of the recommendation and the quality of evidence are provided with each recommendation, using standardized criteria that are applied to all ASCO guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline update.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of the need for any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The review of VTE prophylaxis and treatment identified a total of 35 publications (26 meta-analyses[10-35] and nine RCTs[36-44]) that met eligibility criteria and form the evidentiary basis for the guideline recommendations. The review of VTE risk assessment models identified 18 eligible publications.[45-62] Six included multiple types of cancer,[47,50,53-56] and 12 focused on individual cancer types.[45,46,48,49,51,52,57-62] Seventeen of the studies were prospective or retrospective cohort studies, and one was a pooled analysis of phase II and phase III trials. Characteristics and key results of these publications, by clinical question, are provided in the Data Supplement.

RECOMMENDATIONS

Clinical Question 1

Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

Recommendation 1.1. Hospitalized patients who have active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the

absence of bleeding or other contraindications (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.2. Hospitalized patients who have active malignancy without additional risk factors may be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.3. Routine pharmacologic thromboprophylaxis should not be offered to patients admitted for the sole purpose of minor procedures or chemotherapy infusion, nor to patients undergoing stem-cell/bone marrow transplantation (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review update and analysis. The review included one new publication: a meta-analysis[15] of three RCTs[63-65] that did not focus exclusively on patients with cancer but did report results for the cancer subgroup. Anticoagulation did not significantly reduce the risk of VTE in hospitalized patients with cancer (relative risk [RR], 0.91; 95% CI, 0.21 to 4.0), but the included patients with cancer were heterogeneous with respect to VTE risk, and the sample size of 307 patients with cancer was small. Bleeding information for the cancer subgroup was not available. The main medical conditions required for inclusion in these three RCTs of thromboprophylaxis in hospitalized patients include the following acute conditions: congestive heart failure (acute or class III/IV), acute respiratory illness in the presence of chronic lung disease, acute respiratory failure that did not require ventilator support, acute infection, acute rheumatic disorder, and inflammatory bowel disease. Two of the studies required at least one additional risk factor, such as age 75 years or older, cancer, previous VTE, obesity, varicose veins and/or chronic venous insufficiency, hormone replacement therapy, history of chronic heart failure, chronic respiratory failure, or myeloproliferative syndrome.[63-65]

Clinical interpretation. The inpatient trials enrolled mixed populations, including patients with cancer as well as general medical patients. To date, no trials have evaluated inpatient thromboprophylaxis in a cancer-only population. These recommendations were formulated by extrapolating the best available data in patients without cancer. All RCTs included hospitalized patients with serious medical illness or reduced mobility. The generalizability of these data to all hospitalized patients with cancer is unclear, especially to those who are only admitted for scheduled chemotherapy and are otherwise ambulatory and close to their baseline health status. However, hospitalization is associated with an increased risk of VTE in patients with cancer.[66,67] In addition to experiencing reduced mobility, many hospitalized patients with cancer have additional risk factors for VTE, such as infection or other acute medical conditions or advanced age. Selection of hospitalized patients with cancer at increased risk for VTE based on risk assessment models may enhance the appropriate use of thromboprophylaxis in this setting in the future.[54,55] Further validation of such inpatient VTE risk assessment models are needed to guide inpatient prophylaxis.

Clinical Question 2

Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

Recommendation 2.1. Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer (Type: evidence based; Evidence quality: intermediate to high; Strength of recommendation: strong).

Recommendation 2.2. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) provided there are no significant risk factors for bleeding and no drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting (Type: evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: moderate).

Recommendation 2.3. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review update and analysis. The updated systematic review identified five meta-analyses[12,16,19,31,32] and two more recent RCTs[36,44] that considered primary prophylaxis in patients with cancer in the ambulatory setting.

The five meta-analyses focused primarily on thromboprophylaxis with LMWH. In the 2016 Cochrane review by Di Nisio et al,[16] LMWH reduced the risk of symptomatic VTE by roughly half (RR, 0.54; 95% CI, 0.38 to 0.75) compared with no thromboprophylaxis. In an illustrative high-risk population, this would reduce the risk of symptomatic VTE from 71 per 1,000 patients to 39 per 1,000 patients. LMWH had no significant impact on 1-year mortality (RR, 0.93; 95% CI, 0.80 to 1.09) or risk of major bleeding (RR, 1.44; 95% CI, 0.98 to 2.11) but was associated with an increased risk of clinically relevant bleeding (RR, 3.40; 95% CI, 1.20 to 9.63). Generally similar results were reported in a 2014 review by Ben-Aharon et al,[12] although the result for clinically relevant bleeding was not statistically significant (LMWH *v* control: RR, 1.29; 95% CI, 0.95 to 1.77).

Meta-analyses by Thein et al[31] and Fuentes et al[19] focused on patients with lung cancer. In both publications, LMWH reduced the risk of VTE by roughly half but did not

significantly affect overall survival. The associations between LMWH and bleeding were not statistically significant for major bleeding in Thein et al or total bleeding in Fuentes et al. However, LMWH significantly increased the risk of clinically relevant nonmajor bleeding in Thein et al (RR, 3.35; 95% CI, 2.09 to 5.06).

Tun et al[32] analyzed only patients with advanced pancreatic cancer and reported that LMWH was associated with a decreased risk of symptomatic VTE (RR, 0.18; 95% CI, 0.08 to 0.39) and had a nonsignificant effect on major bleeding (RR, 1.25; 95% CI, 0.48 to 3.31). The bleeding analysis, however, was based on only two trials with a total of 433 patients. Two more recent phase III RCTs[36,44] evaluated DOAC thromboprophylaxis in high-risk ambulatory patients with cancer (Khorana score 2 or higher; see Table 1). AVERT[36] (ClinicalTrials.gov identifier: NCT02048865) assessed apixaban (2.5 mg twice daily) in patients initiating a new course of chemotherapy with a minimum intent of 3 months of therapy. Main exclusion criteria included lesions or conditions at increased risk of clinically significant bleeding, stem-cell transplantation, acute or chronic renal insufficiency with glomerular filtration rate less than 30 mL/min, substantial liver abnormalities, and a platelet count less than 50,000/mm^3. Patients with lymphoma constituted approximately 25% of the study population; otherwise, no other hematologic malignancy was represented by more than 10 patients per trial arm. Objectively documented VTE during a 180-day follow-up period was the primary efficacy outcome. In the AVERT trial, 574 patients were randomly assigned, of whom 563 were included in the modified intention-to-treat (ITT) analysis. Documented VTE occurred in 4.2% of the 288 patients in the apixaban arm and in 10.2% of the 275 patients in the placebo arm (hazard ratio [HR], 0.41; 95% CI, 0.26 to 0.65). During the modified ITT period, major bleeding occurred in 3.5% and 1.8% in the apixaban and the placebo arms, respectively (HR, 2.00; 95% CI, 1.01 to 3.95). During the on-treatment period, major bleeding occurred in 2.1% in the apixaban arm *v* 1.1% in the placebo arm (HR, 1.89; 95% CI, 0.39 to 9.24).

TABLE 1. Predictive Model for Chemotherapy-Associated VTE in the Ambulatory Setting

Patient Characteristic	Points
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal)	1
Prechemotherapy platelet count ≥ 350,000/μL	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/μL	1
Body mass index ≥ 35 kg/m^2	1
Calculate total score, adding points for each criterion in the model	
Interpretation	
High-risk score ≥ 3 points	
Intermediate-risk score = 1-2 points	
Low-risk score = 0 points	

NOTE: Data adapted.[134]
Abbreviation: VTE, venous thromboembolism.

CASSINI[44] (ClinicalTrials.gov identifier: NCT02555878) assessed rivaroxaban (10 mg once daily) in patients with solid tumors or lymphoma starting systemic antineoplastic therapy not limited to cytotoxic chemotherapy. The study required documented absence of DVT on ultrasound screening prior to randomization along with ultrasound monitoring every 8 weeks during the study period. Main exclusion criteria included a diagnosis of primary brain tumors or known history of brain metastases; bleeding diathesis, hemorrhagic lesions, active bleeding, or other conditions with a high risk for bleeding; diagnostically confirmed significant liver disease or dysfunction; evidence of VTE on screening ultrasound or incidental VTE identified on computed tomography scans ordered primarily for staging or restaging of malignancy 30 days or less prior to randomization; and a platelet count less than 50,000/mm^3. Over 50% of study participants had a diagnosis of very high-risk tumor types (pancreatic or gastro-esophageal cancers), and only 7% were patients with lymphoma. The primary efficacy end point was a composite of objectively confirmed lower-extremity proximal DVT, PE, symptomatic upper-extremity or distal lower-extremity DVT, and clearly documented VTE-related death. Among the VTE-screened patients with a Khorana score of 2 or higher, 4.5% were found to have a thrombosis on baseline screening imaging and were not eligible for randomization. Of 841 randomized patients, the primary ITT VTE end point in the 180-day period occurred in 6.0% of 420 patients in the rivaroxaban trial arm and 8.8% of 421 patients in the placebo arm (HR, 0.66; 95% CI, 0.40 to 1.09). In a prespecified analysis of all randomized patients, the primary VTE end point on treatment occurred in 2.6% of 420 and in 6.4% of 421 patients in the rivaroxaban and placebo trial arms, respectively (HR, 0.40; 95% CI, 0.20 to 0.80). The main safety outcome of major bleeding was seen in 2.0% and 1.0% in the rivaroxaban and placebo arms, respectively (HR, 1.96; 95% CI, 0.59 to 6.49). All-cause mortality of 20.0% was observed in the rivaroxaban group compared with 23.8% in the placebo group (HR, 0.83; 95% CI, 0.62 to 1.11). Arterial thromboembolism occurred in 1.0% in the rivaroxaban study arm and 1.7% in the placebo group.

Clinical interpretation. Studies of outpatient thromboprophylaxis span two phases of clinical trials: an initial phase focusing on the efficacy and safety of LMWH in unselected patients with cancer (ie, without risk stratification) and a more recent phase testing DOACs in high-risk patients. However, risk-stratified results of the initial LMWH studies are available.

In the initial phase of unselected patients, the greatest absolute reduction in VTE risk was observed in trials of

patients with advanced pancreatic cancer or selected high-risk populations. Patients with advanced pancreatic cancer have particularly high rates of VTE,[68,69] and two RCTs[70,71] have focused specifically on this patient population but also utilized higher LMWH dosing. The FRAGEM trial (ClinicalTrials.gov identifier: NCT00462852), published in 2012, randomly assigned 123 patients with advanced pancreatic cancer to gemcitabine plus dalteparin or gemcitabine alone.[70] During the 100-day dalteparin treatment period, the addition of dalteparin reduced the risk of VTE from 23% to 3.4% (RR, 0.15; 95% CI, 0.04 to 0.61). Severe hemorrhagic complications occurred in 3.2% of patients treated with gemcitabine alone and 3.4% of patients treated with gemcitabine plus dalteparin. In the 2015 CONKO-004 trial (ClinicalTrials.gov identifier: NCT00785421), 312 patients with advanced pancreatic cancer were randomly assigned to first-line chemotherapy with or without enoxaparin.[71] Risk of symptomatic VTE during the first 3 months was 10.2% without enoxaparin and 1.3% with enoxaparin ($P = .001$). Risk of a major bleed in the first 3 months was 3.4% without enoxaparin and 4.5% with enoxaparin ($P = .64$).[72] Both of these trials used higher-than-standard prophylactic dosing: dalteparin 200 IU/kg once daily for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks in FRAGEM[70] and enoxaparin 1 mg/kg once daily in CONKO-004.[71]

Similar to the pancreas studies, six RCTs of LMWH thromboprophylaxis have been reported in patients with lung cancer, with overall rates of VTE of 7.9% and 4.0% in control and LMWH patients, respectively (RR, 0.51; 96% CI, 0.40 to 0.65) and a nonsignificant increase in major bleeding.[31]

Greater absolute reductions in the risk of VTE were also observed in selected, high-risk patients based on the Khorana risk score.[73] Pooled results from the phase II PHACS study (ClinicalTrial.gov identifier: NCT00876915) and high-risk subgroups (Khorana score 3 or higher) of the two largest phase III studies, PROTECHT and SAVE-ONCO, revealed a reduction in VTE from 8.1% in control patients to 3.3% in LMWH patients (absolute risk difference, 4.3%; 95% CI, 1.5% to 7.1%).[73]

In a newer phase of studies, clinical trials of risk-adapted thromboprophylaxis with DOACs in ambulatory patients with a Khorana score of 2 or higher starting new systemic antineoplastic therapy have been recently published.[36,44] While similar in concept, there are some notable differences in design and outcomes. AVERT focused only on symptomatic VTE or incidental PE events and did not screen for DVT at baseline or during the study. In contrast, CASSINI screened patients at baseline and every 8 weeks during the study using bilateral leg ultrasound. As a result, 4.5% of enrolled patients were not randomized after detection of subclinical proximal DVT. Ultrasound screening likely impacted on symptomatic VTE rates, and a "true" absolute risk reduction in CASSINI is therefore difficult to determine. CASSINI did not require cytotoxic chemotherapy, allowing patients starting other forms of systemic cancer therapy. Patients with primary intracranial malignancies were included in AVERT but excluded in CASSINI. Given the lack of definitive safety data in this population at known high bleeding risk, caution must be exercised. It is noteworthy that the tumor groups represented in the two trials are also different. In AVERT, approximately 50% of the patients had gynecologic cancer or lymphoma, while in CASSINI, approximately 50% had pancreatic or gastric cancer. This difference is highlighted by the 6-month all-cause mortality of 11% and roughly 22%, respectively.

While neither AVERT nor CASSINI were adequately powered for safety end points, a small but consistent absolute increase in major bleeding of approximately 1% in the prophylactic DOAC arm of both studies was observed during the intervention period. There were no between-group differences in overall mortality in the two studies, although in CASSINI, rivaroxaban was associated with a significant reduction in the prespecified composite of the primary outcome combined with all-cause mortality. DOAC use is best avoided if complex drug-drug interactions are anticipated. Rivaroxaban and apixaban should not be used concomitantly with potent inhibitors or inducers of P-glycoprotein or cytochrome P450 3A4.[74,75]

A question raised by these trials is the benefit of screening at baseline for subclinical DVT. In studies of screening patients at high risk for VTE, high rates of baseline DVT have been discovered, ranging from 9% to 12.5% for a Khorana score of 3 or higher to 4.5% for a Khorana score of 2 or higher.[73,76] Some of the differences in outcomes between CASSINI and AVERT may be accounted for by screening. Consideration should be given to whether baseline screening can amplify the effect of thromboprophylaxis in high-risk ambulatory patients with cancer.

A risk-adapted approach to thromboprophylaxis in ambulatory patients receiving cancer treatment should be accompanied by a discussion with patients of the balance between absolute benefits and harms as well as the uncertainty surrounding duration of prophylaxis.

Clinical Question 3

Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

Recommendation 3.1. All patients with malignant disease undergoing major surgical intervention should be offered pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) or LMWH unless contraindicated because of active bleeding, or high bleeding risk, or other contraindications (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. Prophylaxis should be commenced preoperatively (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3. Mechanical methods may be added to pharmacologic thromboprophylaxis but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because of active bleeding or high bleeding risk (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.4. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.5. Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 to 10 days. Extended prophylaxis with LMWH for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high-risk features, such as restricted mobility, obesity, history of VTE, or with additional risk factors. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate to strong).

Literature review update and analysis. The updated systematic review included three RCTs[38,40,41] and four meta-analyses.[11,17,18,27]

Recommendation 3.5 was revised to recommend extended thromboprophylaxis for selected patients undergoing either open or laparoscopic abdominal or pelvic surgery. The addition of laparoscopic surgery to the recommendation was prompted by a 2014 RCT by Vedovati et al[41] in which 225 patients undergoing laparoscopic surgery for colorectal cancer were randomly assigned to 4 weeks or 1 week of thromboprophylaxis with LMWH. By 4 weeks after surgery, VTE had occurred in 9.7% of patients in the 1-week arm and no patients in the 4-week arm. During the same time period, major bleeding occurred in 1 patient in the 1-week arm and no patients in the 4-week arm. Support for extended thromboprophylaxis in patients undergoing abdominal or pelvic surgery was also provided by a 2018 meta-analysis by Felder et al[18] and a 2016 meta-analysis by Fagarasanu et al.[17]

The other RCTs and meta-analyses addressed a mix of questions, including dosing schedules and disease site–specific clinical scenarios. In an RCT of 111 patients undergoing esophagectomy, Song et al[40] compared nadroparin twice a day with nadroparin once a day starting 6 hours after surgery and continuing until the seventh postoperative day. Nadroparin twice a day reduced the risk of VTE (0% *v* 9%; *P* = .03). The addition of LMWH to intermittent pneumatic compression was evaluated in an RCT of patients undergoing gastrectomy for gastric adenocarcinoma.[38] Compared with pneumatic compression alone, the combination of pneumatic compression and LMWH reduced the risk of VTE but increased the risk of bleeding. A 2018 Cochrane review by Matar et al[27] compared LMWH with UFH for perioperative thromboprophylaxis in patients with cancer undergoing surgical intervention. There were no significant differences in risk of PE, DVT, mortality, or bleeding, though LMWH is recommended over UFH for extended prophylaxis in the ambulatory setting. The 2018 Cochrane review also compared LMWH with fondaparinux based on three RCTs in the perioperative setting. The two agents did not differ significantly with respect to risk of VTE or major bleeding, but the certainty of evidence was low. Finally, the safety and efficacy of thromboprophylaxis in patients undergoing craniotomy was evaluated in a 2016 meta-analysis by Alshehri et al.[11] Risk of VTE was reduced by UFH (compared with placebo) and by the addition of LMWH to mechanical prophylaxis (compared with mechanical prophylaxis alone). However, the bleeding analysis included studies with a mix of intervention and control arms, making it difficult to draw clear conclusions.

Clinical interpretation. Recent studies have shown that the risk of VTE persists several weeks after abdominopelvic cancer surgery. Based on data from the Computerized Registry of Patients with Venous Thromoembolism (RIETE), Bustos Merlo et al[77] have shown that in patients who suffered postoperative VTE, it was detected after hospital discharge in 54% of the cases. Colorectal and genitourinary cancer, as well as those patients who received radiotherapy, had a significantly higher risk of postdischarge VTE.

Based on the data provided by Vedovati et al,[41] and the results from the meta-analyses by Felder et al[18] and Fagarasanu et al,[17] there is additional evidence that for patients undergoing either laparoscopic or open surgery for abdominal and pelvic cancer, extending the administration of LMWH for 30 days after the day of surgery reduces the risk of VTE. It is important to notice that this reduction in VTE was not associated with an increase in bleeding complications.

A systematic review and meta-analysis by Guo et al[78] also concluded that extended pharmacologic prophylaxis with LMWH significantly reduces VTE after cancer surgery with a nonsignificant increase in bleeding complications. Other lower-quality studies have provided similar results in urologic oncology surgery,[79] after radical cystectomy for bladder cancer surgery,[80,81] and in liver resection for cancer.[82]

In lung cancer surgery, the results of the cohort study by Hachey et al[83] suggested that the application of a revised Caprini risk assessment model could be helpful to select patients who would benefit from extended prophylaxis. Similarly, another more recent study by Sterbling et al[84] concluded that the use of the risk assessment model to guide prophylaxis decisions decreases the rate of symptomatic VTE without increasing the incidence of bleeding complications in thoracic surgery patients with cancer.

Clinical Question 4

What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

Recommendation 4.1. Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance < 30 mL/min) (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.2. For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKAs). VKAs are inferior, but may be used if LMWH or DOACs are not accessible. There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a DOAC (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.3. Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak to moderate).

Recommendation 4.4. Based on expert opinion in the absence of randomized trial data, uncertain short-term benefit, and mounting evidence of long-term harm from filters, the insertion of a vena cava filter should not be offered to patients with established or chronic thrombosis (VTE diagnosis more than 4 weeks ago), nor to patients with temporary contraindications to anticoagulant therapy (eg, surgery). There also is no role for filter insertion for primary prevention or prophylaxis of PE or DVT due to its long-term harm concerns. It may be offered to patients with absolute contraindications to anticoagulant therapy in the acute treatment setting (VTE diagnosis within the past 4 weeks) if the thrombus burden was considered life-threatening. Further research is needed (Type: informal consensus; Evidence quality: low to intermediate; Strength of recommendation: moderate).

Recommendation 4.5. The insertion of a vena cava filter may be offered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal anticoagulant therapy. This is based on the panel's expert opinion given the absence of a survival improvement, a limited short-term benefit, but mounting evidence of the long-term increased risk for VTE (Type: informal consensus; Evidence quality: low to intermediate; Strength of recommendation: weak).

Recommendation 4.6. For patients with primary or metastatic CNS malignancies and established VTE, anticoagulation as described for other patients with cancer should be offered, although uncertainties remain about choice of agents and selection of patients most likely to benefit (Type: informal consensus; Quality of evidence: low; Strength of recommendation: moderate).

Recommendation 4.7. Incidental PE and DVT should be treated in the same manner as symptomatic VTE, given their similar clinical outcomes compared with patients with cancer with symptomatic events (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 4.8. Treatment of isolated subsegmental PE or splanchnic or visceral vein thrombi diagnosed incidentally should be offered on a case-by-case basis, considering potential benefits and risks of anticoagulation (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review update and analysis. Recent meta-analyses confirmed previous findings that LMWH is more effective than VKAs at reducing the risk of recurrent VTE in patients with cancer.[14,23,26,28] A meta-analysis of LMWH versus UFH for the initial treatment of VTE reported no significant differences in risk of recurrent VTE (RR, 0.69; 95% CI, 0.27 to 1.76) or mortality (RR, 0.66; 95% CI, 0.40 to 1.10).[21] LMWH versus VKAs among patients with cancer with renal impairment was evaluated in a subgroup analysis of the CLOT trial.[42] Patients in the dalteparin arm had a reduced risk of recurrent VTE compared with the VKA arm (2.7% *v* 17%; HR, 0.15; 95% CI, 0.03 to 0.65). Risk of major bleeding did not differ significantly between the two arms (9.5% *v* 6.9%; HR, 1.29; 95% CI, 0.43 to 3.82).

DOACs were compared with LMWH in two RCTs in patients with cancer,[39,43] a meta-analysis of these two trials,[25] and two meta-analyses of trials that included subsets of patients with cancer.[13,28] In an open-label, noninferiority trial, Raskob et al[39] randomly assigned 1,050 patients with cancer with acute symptomatic or incidental VTE to at least 6 months of treatment with either edoxaban or dalteparin. The primary outcome was a composite measure of recurrent VTE and major bleeding during 12 months of follow-up. Edoxaban was noninferior to dalteparin: A primary outcome event occurred in 12.8% of patients in the edoxaban arm and 13.5% of patients in the dalteparin arm (HR, 0.97; 95% CI, 0.70 to 1.36; $P = .006$ for noninferiority; $P = .87$ for superiority). When VTE recurrence and major bleeding were considered separately, the risk of VTE recurrence was not significantly different between the two arms (7.9% with edoxaban *v* 11.3% with dalteparin; HR, 0.71; 95% CI, 0.48 to 1.06), but the risk of major bleeding was higher with edoxaban (6.9% *v* 4%; HR, 1.77; 95% CI, 1.03 to 3.04). The

increased risk of major bleeding with edoxaban was particularly apparent among patients with GI malignancies: Among patients with a GI malignancy, 12.7% of patients in the edoxaban arm experienced major bleeding compared with 3.6% of patients in the dalteparin arm ($P = .005$).[85]

The SELECT-D trial (Clinical trial information: ISRCTN86712308) by Young et al[43] randomly assigned 406 patients with active cancer and VTE to 6 months of treatment with either rivaroxaban or dalteparin. In this pilot study using post hoc adjudication for the primary outcome of symptomatic VTE, the 6-month risk of VTE recurrence was 4% with rivaroxaban and 11% with dalteparin (HR, 0.43; 95% CI, 0.19 to 0.99). Risk of major bleeding was not significantly different between study arms (6% with rivaroxaban *v* 4% with dalteparin; HR, 1.83; 95% CI, 0.68 to 4.96), but the risk of clinically relevant nonmajor bleeding was higher with rivaroxaban (13% with rivaroxaban *v* 4% with dalteparin; HR, 3.76; 95% CI, 1.63 to 8.69). During an interim safety analysis, a nonsignificant difference in major bleeding noted between study arms in patients with esophageal or gastroesophageal cancer prompted a protocol amendment to exclude these patients from enrollment. Among these patients, major bleeding occurred in four (36%) of 11 patients treated with rivaroxaban and one (5%) of 19 patients treated with dalteparin.

In a meta-analysis[25] of the trials by Raskob[39] and Young,[43] DOACs were associated with a numerically lower risk of VTE (RR, 0.65; 95% CI, 0.42 to 1.01) but a higher risk of major bleeding (RR, 1.74; 95% CI, 1.05 to 2.88) compared with LMWH. There was no significant difference in mortality (RR, 1.03; 95% CI, 0.85 to 1.26).

A meta-analysis by Brunetti et al[13] analyzed two RCTS of hospitalized patients that included a subset of patients with cancer; DOACs were similar to LMWH with respect to recurrent VTE (odds ratio [OR], 0.96; 95% CI, 0.52 to 1.75) but had a higher risk of bleeding (OR, 2.72; 95% CI, 1.05 to 7.01). Posch et al[28] conducted a network meta-analysis with an indirect comparison between DOACs and LMWH; neither recurrent VTE nor bleeding differed significantly between treatment arms.

Nine meta-analyses[13,14,20,23,24,28,29,33,34] compared DOACs with VKAs in studies that did not restrict to patients with cancer but did report on the cancer subgroup. DOACs included rivaroxaban, apixaban, dabigatran, and edoxaban. With the exception of a 2014 meta-analysis that reported a reduced risk of major bleeding with rivaroxaban,[29] risk of recurrent VTE and risk of major bleeding did not differ significantly between treatment arms. Of note, most of the accrued patients with cancer in non–cancer-specific DOAC trials did not have active malignancy. Most of these patients only had a history of cancer or had completed cancer chemotherapy. Therefore, the results of non–cancer-specific DOAC trials should be considered with caution.

In the cancer-specific DOAC trials, DOACs were commenced when the next dose of LMWH would have been due.

Clinical interpretation. Contraindications to therapeutic anticoagulation are listed in Table 2.

DOACs. Oral anticoagulants that target thrombin (direct thrombin inhibitor, dabigatran) or activated factor X (antifactor Xa inhibitors, rivaroxaban, apixaban, and edoxaban) are now approved for treatment of DVT or PE as well as for DVT prophylaxis following orthopedic surgery and for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In the current update, edoxaban and rivaroxaban have been added as VTE treatment options based on evidence from two RCTs.[39,43] Apixaban and dabigatran do not have published data in comparison with LMWH in the therapeutic setting and are not recommended in the cancer setting until efficacy and safety data are available.

Particular caution for DOAC use is warranted in settings associated with an increased risk for bleeding. Patients with additional risk factors for bleeding, such as use of antiplatelet agents, renal or hepatic impairment, thrombocytopenia, or prior history of GI bleeding, should be appropriately counseled. Patients with unresected mucosal tumors or active mucosal lesions may experience more bleeding with DOACs than with LMWH. Limited safety data exist for DOAC use in patients requiring cancer surgery and in those with primary CNS malignancies or untreated brain metastases.

Due to the increased risk for major bleeding events with DOAC compared with LMWH when treating existing VTE, LMWHs are currently preferred in settings with an increased risk for bleeding. Data from recent and ongoing trials and real-world practice over time may provide more specific information in these more vulnerable higher-risk or sicker patient populations, who were mostly excluded from clinical trial participation.

Another important safety consideration in using any DOAC in patients with cancer is the potential for drug-drug interaction and GI absorption and tolerability with anticancer treatments, including chemotherapeutic agents, hormonal therapy, and immunotherapy. Potent inhibitors or inducers of P-glycoprotein can interact with edoxaban and rivaroxaban, and potent inhibitors or inducers of cytochrome P450 34A can interact with rivaroxaban.[74,75] Additional clinically important drug-drug interaction data may emerge over time. Nausea or vomiting may also impact adherence with use of DOACs given their oral route of administration.[86]

Treatment beyond 6 months. There is limited information about the risks and benefits of anticoagulation beyond 6 months in patients with cancer. However, it is the consensus of the Expert Panel, based on extrapolation from patients with unprovoked VTE, that continuing anticoagulation beyond 6 months should be considered for selected patients because of the persistent high risk of recurrence in those with active cancer. The decision to continue anticoagulation must be balanced against the risk

TABLE 2. Contraindications to Therapeutic Anticoagulant Therapy in Patients With Cancer

Contraindications
Absolute contraindications*
Non-DOACs and DOACs
Active major, serious, or potentially life-threatening bleeding not reversible with medical or surgical intervention, including but not limited to any active bleeding in a critical site (eg, intracranial, pericardial, retroperitoneal, intraocular, intra-articular, intraspinal)
Severe, uncontrolled malignant hypertension
Severe, uncompensated coagulopathy (eg, liver failure)
Severe platelet dysfunction or inherited bleeding disorder
Persistent, severe thrombocytopenia (< 20,000/μL)
High-risk invasive procedure in a critical site, including but not limited to lumbar puncture, spinal anesthesia, epidural catheter placement
DOAC specific
Concurrent use of potent P-glycoprotein or CYP3A4 inhibitors or inducers
Relative contraindications†
Non-DOACs and DOACs
Intracranial or spinal lesion at high risk for bleeding‡§
Active GI ulceration at high risk of bleeding‡§
Active but non–life-threatening bleeding (eg, trace hematuria)‡§
Intracranial or CNS bleeding within past 4 weeks‡§
Recent high-risk surgery or bleeding event‡§
Persistent thrombocytopenia (< 50,000/μL)‡§
Patients for whom anticoagulation is of uncertain benefit
Patient receiving end-of-life/hospice care
Very limited life expectancy with no palliative or symptom reduction benefit
Asymptomatic thrombosis with concomitant high risk of serious bleeding
Patient characteristics and values
Preference or refusal
Nonadherence to dosing schedule, follow-up, or monitoring

NOTE. These criteria are specific for therapeutic doses of anticoagulation and should not be applied to prophylactic doses of anticoagulation. Please refer to the DOAC section in the text for additional safety considerations. The following settings also do not have adequate safety data for DOAC use, such as most high-risk bleeding settings, including but not necessarily limited to active mucosal bleeding, active mucosal tumors (given the observed increased bleeding risk in such settings, especially mucosal areas that absorb or renally clear the drug) such as GI and genitourinary malignancies prior to definitive cancer surgery, hemorrhagic malignant and nonmalignant lesions, intracranial or CNS bleeding within past 4 weeks, serious nausea or vomiting precluding adequate oral DOAC intake, or conditions limiting drug absorption in general. Additional potential contraindications exist for DOAC, including nonhealed surgical site in the perioperative period; trauma conferring a high bleeding risk; minor hemorrhagic malignant or nonmalignant lesions; treated brain metastases, other CNS malignancies, or the use of cyberknife; presence of lesser drug-drug interactions potentially impacting drug efficacy or safety; anticipated nausea or vomiting impacting oral DOAC intake; and obesity (body mass index > 40 kg/m^2 or a weight of > 120 kg).

Abbreviation: DOAC, direct oral anticoagulant.

*Absolute contraindications are situations in which anticoagulation should not be given because the risk of harm associated with bleeding is very likely to exceed the potential benefit from anticoagulation.

†Relative contraindications are situations in which anticoagulation may be given if the risk of recurrent or progressive thrombosis is estimated to exceed the risk of bleeding. Due to DOACs' increased risk for major bleeding events compared with low-molecular-weight heparins (LMWHs) in the venous thromboembolism treatment setting, LMWHs are generally the preferred agents in settings with an increased bleeding risk, especially in settings of relative contraindications. Patient preferences also need to be taken into consideration when making anticoagulation choices.

‡There is limited evidence regarding the safety of DOAC use in this setting.

§The panel was not unanimous in the decision to list these as relative contraindications for DOAC, as we do not have adequate safety data in these clinical settings. Given the known increased risk in major and clinically relevant nonmajor bleeding for DOACs compared with LMWHs in the venous thromboembolism treatment setting, these relative contraindications for non-DOAC anticoagulants may be considered absolute contraindications for DOAC use in some patients.

of bleeding, cost of therapy, quality of life, life expectancy, and patient preference. In the single-arm DALTECAN trial (ClinicalTrials.gov identifier: NCT00942968),[87] patients with cancer with VTE received extended treatment with dalteparin. Of 334 patients enrolled, 109 completed 12 months of dalteparin. Risk of major bleeding was greatest during the first month of treatment (3.6%), declining to 1.1% per patient-month during months 2 to 6 and 0.7% during months 7 to 12. Risk of recurrent VTE was 5.7% during month 1, 3.4% during months 2 to 6, and 4.1% during months 7 to 12. Use of LMWH beyond 6 months was also evaluated in the single-arm TiCAT trial.[88] Of 247 patients enrolled, 136 completed 12 months of tinzaparin. The rate of clinically relevant bleeding was 0.9% per patient-month during months 1 through 6 and 0.6% during months 7 through 12.

Recurrent VTE while receiving anticoagulation. Patients with recurrent VTE despite standard doses of anticoagulant therapy should be assessed for treatment compliance, heparin-induced thrombocytopenia, or any evidence of mechanical compression resulting from malignancy. Management options include treatment with an alternative anticoagulant regimen or increasing the dose of LMWH. Adding a vena cava filter to LMWH should be reserved as a last resort given its absence of a survival benefit and an increased long-term risk for VTE development. In patients for whom standard doses of LMWH fail, higher doses should be considered first if the clinical setting and renal function allow. Evidence to support these strategies is limited. To provide information on outcomes after recurrent VTE, an international registry collected information about 212 patients with cancer and recurrent VTE despite anticoagulant therapy.[89] Seventy percent of patients were on LMWH and 27% were on a VKA. Twenty-eight percent of patients were receiving a subtherapeutic dose. Eleven percent of patients had additional VTE recurrences, and 8% had major bleeding during 3 months of follow-up. Additional recurrences were less common with LMWH than with VKAs (HR, 0.28; 95% CI, 0.11 to 0.70) and similar among those who had unchanged or increased anticoagulant intensity (HR, 1.09; 95% CI, 0.45 to 2.63). Smaller observational studies have also reported on treatment and outcomes among patients with cancer with recurrent VTE.[90,91] The potential for selection bias and confounding limits inferences from all of these retrospective studies. There are currently no data evaluating whether switching DOAC agents or altering doses is helpful in this setting.

Incidental VTE. Incidental findings of PE and/or DVT during routine staging with computed tomography scans of the abdomen and pelvis are frequently reported, as are splanchnic or visceral vein thrombi. In general, rates of VTE recurrence, bleeding, and mortality seem to be similar in patients with cancer and incidental VTE compared with those with symptomatic VTE.[92-96]

Optimal management of incidental splanchnic vein thrombosis remains uncertain. A registry-based study evaluated 177 patients with incidental splanchnic vein thrombosis, 35% of whom had solid tumors.[97] The prognosis of incidental splanchnic vein thrombosis was generally similar to that of clinically suspected splanchnic vein thrombosis. Furthermore, in multivariable analysis among the patients with incidental splanchnic vein thrombosis, anticoagulant treatment reduced the risk of thrombotic events without increasing the risk of major bleeding.

An analysis of the international RIETE registry reported on 521 patients with splanchnic vein thrombosis, 45% of whom had cancer.[98] Overall, 212 cases (41%) were symptomatic. Most patients (93%) received anticoagulant therapy. During anticoagulant therapy, patients with incidental splanchnic vein thrombosis had a nonsignificantly higher rate of symptomatic VTE recurrence than patients with symptomatic splanchnic vein thrombosis (HR, 2.04; 95% CI, 0.71 to 5.88) and a similar rate of major bleeding (HR, 1.12; 95% CI, 0.47 to 2.63). Patients with active cancer had an increased risk of VTE recurrence (HR, 3.06; 95% CI, 1.14 to 8.17). Overall, rates of major bleeding were higher than rates of VTE recurrence.

Questions also remain about the need for anticoagulation in patients with isolated, incidental subsegmental PE. Isolated incidental subsegmental PE found on staging scans can represent imaging artifact and should be reviewed with the radiologist. In a pooled analysis of 926 patients with cancer with incidental PE, risk of recurrence was similar in patients with subsegmental versus more proximally located PE.[99] The analysis was not able to address isolated cases specifically.

Vena cava filter. The role of inferior vena cava (IVC) filters remains uncertain and controversial because of the paucity of trials. In an 8-year follow-up report from the only RCT of permanent IVC filters, the addition of IVC filters to standard anticoagulation for at least 3 months compared with anticoagulation alone reduced the risk of PE but increased the incidence of DVT and had no effect on survival.[100] Patients with cancer constituted 16% and 12% of those with and without filters, respectively. In a small RCT comparing fondaparinux alone for 90 days with fondaparinux and IVC filter placement, no difference in recurrent VTE, bleeding, or mortality was found.[101] In patients with contraindications to anticoagulant therapy, there are no randomized clinical trial data to guide therapy, but there is mounting evidence of long-term harm from filters in nonrandomized studies. Cohort studies in patients with cancer suggest much higher long-term rates of recurrent VTE and the absence of a survival advantage with filters.[102,103] Increased 30-day mortality among IVC filter recipients was reported in a recent large retrospective cohort study of hospitalized patients with VTE and a contraindication to anticoagulation.[104] Thirty-six percent of patients in this cohort had cancer. As patients with cancer have higher VTE rates compared with patients without cancer, it remains questionable whether there is any

improved short-term benefit with filter placement in patients with cancer who have contraindications to anticoagulant therapy. Further studies are needed, particularly RCTs.

Another question regarding filters is whether permanent or retrievable filters are preferable in the cancer setting. It is reasonable to select a retrievable filter when the contraindication to anticoagulation is expected to be transient. The safety, however, of IVC filters has raised serious concerns regarding the long-term risk of VTE. In 2010 and 2014, the US Food and Drug Administration released safety alerts for optional recovery filters in response to the high number of adverse events reported.[105]

Intracranial malignancy. Previously, the recommendation regarding VTE treatment in patients with CNS malignancies focused only on patients with primary CNS malignancies. The recommendation now includes patients with metastatic CNS malignancies. Observational data suggest that patients with CNS metastases have a lower risk of intracranial bleeding on pharmacologic anticoagulation than patients with primary CNS malignancies.

Patients with intracranial tumors are at increased risk for thrombotic complications and intracranial hemorrhage (ICH), but the presence of a stable or active primary intracranial malignancy or brain metastases is not an absolute contraindication to anticoagulation. Limited data suggest that therapeutic anticoagulation does not increase ICH risk among patients with brain metastases but may increase risk among patients with primary brain tumors.[106-110] Lack of long-term anticoagulation, however, has been associated with an increased risk of recurrent VTE in patients with glioblastoma.[111] Furthermore, a high failure rate has been reported with IVC filters, without improved survival or reduced ICH in small retrospective series.[112-114] A recent meta-analysis concluded that therapeutic anticoagulation should be considered in patients with brain tumors with thrombosis. Treatment-related ICH appeared to be less common in metastatic tumors (whether associated with baseline hemorrhage) than in gliomas.[108] Preliminary data from a retrospective cohort of patients with metastatic brain disease and venous thrombosis suggest that DOACs may be associated with a lower risk of ICH than LMWH in this population.[110]

Special populations. Evidence on LMWH and other anticoagulants in special patient populations comes largely from patients without cancer. Most studies were retrospective, had small samples, and did not include appropriate control groups. Although increasing age is a risk factor for bleeding, anticoagulant therapy should be offered to elderly patients who have no contraindications. Caution and close monitoring are necessary in those with renal impairment, fall risk, cognitive decline or poor functional status and without family or medical support.

Renal impairment. Bleeding risk is high in patients with renal impairment and likely even higher in those with concurrent cancer. Limited data suggest that LMWH can accumulate when therapeutic doses are administered to patients with creatinine clearance less than 30 mL/min and that the risk of bleeding in these patients is at least twofold higher than in patients with normal creatinine clearance.[115] Studies indicate that enoxaparin requires dose reduction, but tinzaparin may not.[116-118] Secondary analyses of the CLOT[42] and CATCH (ClinicalTrials.gov identifier: NCT01130025)[119] trials evaluated the efficacy and safety of LMWHs for preventing recurrent VTE in patients with cancer and renal impairment. The CATCH trial randomly assigned patients with cancer-associated thrombosis to tinzaparin (175 IU/kg once daily) or warfarin for 6 months.[119] Renal impairment at baseline (glomerular filtration rate less than 60 mL/min/1.73 m^2) was found in 131 (15%) of 864 patients. Patients with renal impairment had higher rates of recurrent VTE and major bleeding than patients without renal impairment. Among patients with renal impairment, outcomes did not vary significantly by treatment arm (tinzaparin or warfarin), although the study was not powered to detect subgroup differences between treatment arms. Anti-Xa measurements were not routinely performed. The CLOT trial randomly assigned patients with cancer-associated thrombosis to dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily for 5 months) or VKA. Renal impairment at baseline (creatinine clearance $<$ 60 mL/min) was found in 162 (24%) of 676 patients. Among the patients with renal impairment, recurrent VTE occurred in 2.7% of patients treated with dalteparin and 17% of patients treated with VKA ($P = .01$). Bleeding rates did not vary significantly by treatment arm. Elevated anti-Xa levels led to a reduction in the dose of dalteparin in one of 74 patients enrolled with renal impairment at baseline. Anti-Xa measurement is recommended if LMWH is used in patients with moderate to severe renal impairment. If this is not available, UFH and VKAs are safer options for initial and long-term treatment, respectively.

The safety and dosing data for DOACs regarding renal and liver dysfunction have not been studied in detail and are evolving with more extensive real-world use. Please refer to the US Food and Drug Administration package inserts for the most current dosing information.

Obesity. In large or obese patients, LMWH dosing has not been well studied. Cohort studies using enoxaparin and dalteparin suggest that LMWH dose should be based on a person's actual body weight.[120,121] Bleeding risk does not appear to be higher in obese patients. There is uncertain, very early data regarding DOAC dosing in obese patients and no data regarding the clinical benefit of DOAC laboratory assessment. Therefore, the panel consensus is to use caution with DOAC in patients weighing over 120 kg. Currently, LMWH is likely the preferred option in this setting. Based on a guidance statement from the International Society on Thrombosis and Haemostasis, available subgroup analyses of RCTs performed in patients without cancer suggest that standard DOAC dosing is efficacious and safe compared with VKAs for patients weighing 120 kg

or less or with a body mass index of 40 kg/m^2 or less.[122] The International Society on Thrombosis and Haemostasis recommends that DOACs be avoided in those above these weight parameters because very few of these patients were enrolled in the definitive RCTs, and pharmacokinetic/pharmacodynamic studies in volunteers at extreme weights suggest decreased drug exposure, reduced peak concentrations, and shorter half-lives. If DOACs need to be used in patients with a body mass index greater than 40 kg/m^2 or a weight of greater than 120 kg, then drug-specific peak and trough levels are advised despite the uncertainty surrounding their clinical utility at this time. If the levels are within the expected range, it is likely reasonable to continue DOACs. If the levels are outside the expected range, it is prudent to switch to another anticoagulant. It should be noted that there are no defined therapeutic ranges for DOACs and that there is high interpatient variability also among normal weight patients for a given dose.[122] Few DOAC trials specifically performed in patients with cancer included patients with extreme weights. Further data are needed prior to the routine use of DOACs in this setting.

Clinical Question 5

Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?

Recommendation 5. Anticoagulant use is not recommended to improve survival in patients with cancer without VTE (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. The updated literature review included one RCT[37] and three meta-analyses[10,22,35] that focused on anticoagulation in relation to survival in patients with cancer who did not have an indication for anticoagulation. The RASTEN trial (ClinicalTrials.gov identifier: NCT00717938)[37] evaluated the addition of enoxaparin to standard treatment in 390 patients with small-cell lung cancer. Enoxaparin was administered at a half-therapeutic dose (1 mg/kg subcutaneously daily) but had no significant effect on overall survival (HR, 1.11; 95% CI, 0.89 to 1.38) or progression-free survival (HR, 1.18; 95% CI, 0.95 to 1.46). In the 2017 Cochrane review of oral anticoagulants by Kahale et al,[22] neither VKAs nor DOACs were significantly associated with mortality, although the DOAC result was based on only a single small trial. Parenteral anticoagulants were assessed in a separate 2017 Cochrane review by Akl et al,[10] which reported no significant association between heparin (either UFH or LMWH) and mortality at 12 or 24 months. Yu et al[35] focused specifically on lung cancer and reported reduced mortality with heparin (HR, 0.71; 95% CI, 0.60 to 0.84).

Clinical interpretation. While further RCTs address the potential survival impact of anticoagulation in patients with cancer, there remain no such studies of DOACs at the present time.

Clinical Question 6

What is known about risk prediction and awareness of VTE among patients with cancer?

Recommendation 6.1. There is substantial variation in risk of VTE between individual patients with cancer and cancer settings. Patients with cancer should be assessed for VTE risk initially and periodically thereafter, particularly when starting systemic antineoplastic therapy or at the time of hospitalization. Individual risk factors, including biomarkers or cancer site, do not reliably identify patients with cancer at high risk of VTE. In the ambulatory setting among patients with solid tumors treated with systemic therapy, risk assessment can be conducted based on a validated risk assessment tool (Khorana score; Table 1) (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.2. Oncologists and members of the oncology team should educate patients regarding VTE, particularly in settings that increase risk, such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Literature review update and analysis. Since the last update of these guidelines, five additional cohort studies evaluated the Khorana score in patients with a mix of cancer types. Patients with higher Khorana scores had higher risks of VTE in two prospective studies of ambulatory patients with cancer[50,56] and a prospective study of patients with cancer undergoing insertion of a central venous port.[47] In the central venous port study, the association between Khorana score and catheter-related VTE was of borderline significance (OR, 3.50; 95% CI, 1.00 to 12.30).[47] Patell et al[55] applied the score to hospitalized patients with cancer and reported that patients with a high Khorana score ($\geq$ 3) were significantly more likely than patients with a low risk score to develop VTE during hospitalization (multivariable OR, 2.52; 95% CI, 1.31 to 4.86). Similar results were reported in a multicenter retrospective study of 1,398 hospitalized patients.[54] In this analysis, in-hospital VTE occurred in 5.4% (95% CI, 1.9% to 8.9%) of high-risk patients, 3.2% (95% CI, 2.0% to 4.4%) of intermediate-risk patients, and 1.4% (95% CI, 0.3% to 2.6%) of low-risk patients (OR for high- *v* low-risk patients, 3.9; 95% CI, 1.4 to 11.2).

Multiple modifications of the Khorana score as well as new risk assessment tools have been proposed, including PROTECHT[123] Vienna,[124] CONKO-004,[125] ONKOTEV,[126] COMPASS-CAT,[127] and Tic-Onco.[128] A 2017 cohort study attempted to compare efficacy of some of these tools, but 70% of patients were enrolled up to 3 months after the start of therapy, which nullifies the utility of the components of these scores that rely on baseline variables prior to the start of chemotherapy.[129] More recently, Pabinger et al[53] reported on the development and validation of a tool that utilizes only two

variables: type of cancer and D-dimer levels, with varying cutoffs of the latter for different types of cancers. Further data are awaited on whether this new tool is also predictive of benefit from thromboprophylaxis.

Assessment of the Khorana score in studies of individual cancer types produced mixed results. No significant association between Khorana score and VTE risk was reported in three studies of lung cancer,[49,51,59] two studies of pancreatic cancer,[48,52] one study of hepatocellular carcinoma,[62] and one study of gastric cancer.[46] Only one of these studies was prospective.[49] It is possible that the data quality limitations of retrospective studies, the nonavailability of laboratory data within 2 weeks of the chemotherapy start, and other potential limitations such as limited number of patients might have contributed to these results given the abundance of prospective data, including clinical trial data, that have validated the Khorana score outside of lung cancer. A retrospective study of patients with metastatic urothelial cancer reported no overall association between Khorana score and VTE risk but did find an early association (during the first 3 months after initiation of chemotherapy).[57] In lymphoma, a pooled analysis of phase II and phase III trials reported a significant association between Khorana score and risk of VTE,[60] but a smaller retrospective study did not.[58] Both studies of germ cell tumors reported a significant association between Khorana score and VTE risk.[45,61]

Five of the studies of individual tumor types also evaluated other approaches to VTE risk assessment. In germ cell tumors, categories of retroperitoneal lymph node size[61] and stage[45] were each associated with VTE risk. In lung cancer, COMPASS-CAT best distinguished between patients at low or high risk of VTE.[59] In advanced pancreatic cancer, neither the CONKO score nor the activated partial thromboplastin time was significantly associated with risk.[48] In gastric cancer, neither the platelet-to-lymphocyte ratio nor the neutrophil-to-lymphocyte ratio was significantly associated with VTE.[46]

Clinical interpretation. Multiple cancer-, treatment-, and patient-related risk factors for VTE relevant to various cancer populations have been identified.[124,130-132] However, recent data have validated and established formal risk assessment tools to identify risk of VTE in patients with cancer in various settings.[133] The Khorana score for VTE was initially developed and internally validated in a cohort of ambulatory patients with solid tumor diagnoses initiating systemic chemotherapy (Table 1) followed for four cycles of therapy.[134] These results were then validated by multiple, independent, external validation studies as discussed previously and in the prior ASCO guideline on cancer-associated thrombosis. This tool has also been shown to predict for benefit of thromboprophylaxis[73,123] in patients with a risk score of 3 or higher in subgroup and/or pooled analyses, to identify patients for education regarding VTE,[50] and to target patients for early detection of VTE.[73,76] Two recent thromboprophylaxis trials were restricted to patients with a Khorana score of 2 or higher.[36,44] Multiple additional cohort studies are evaluating validation of techniques to further refine current risk stratification approaches or to develop new models that incorporate genetic factors or coagulation-specific biomarkers; results of these studies could alter our approach to risk stratification in the future.

ANTICOAGULANT DOSING

Information about anticoagulant dosing in prophylactic and treatment settings is provided in Table 3.

PATIENT AND CLINICIAN COMMUNICATION

Despite the well-known association of VTE and cancer, patient awareness of the risk and warning signs of VTE remains low,[135,136] highlighting the need for increased patient education and awareness. Oncologists, oncology nurses, and other health care professionals on the oncology team should ensure, at a minimum, that patients have a basic recognition of VTE warning signs. Further education can help patients to distinguish among symptoms secondary to their underlying disease, treatment, and other potential causes. Patients may not report new symptoms unless questioned directly because they mistakenly assume that symptoms are manifestations of their cancer or adverse effects of therapy. A good patient history, along with ongoing communication with the health care team, can help to ensure effective communication and facilitate patient understanding. For recommendations and strategies to optimize general patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[137]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[138-140] Rates of VTE may differ by race and ethnicity. Indeed, a recent review of guidelines for unprovoked VTE treatment suggests that findings may not be generalizable to racially and ethnically diverse patient populations.[141] Specifically related to VTE in cancer, some studies suggest greater risk of VTE in black patients with cancer and lower risk in Asian patients with cancer.[142-144] In an analysis of the SAVE-ONCO thromboprophylaxis trial control arm, after adjustment for baseline characteristics, the risk of VTE in black patients was more than three times

TABLE 3. Dosing Regimens for Prophylaxis/Treatment of VTE in Patients With Cancer

Clinical Setting	Drug	Regimen[a]
Pharmacologic (anticoagulant) prophylaxis		
Hospitalized medical patients[b]	UFH	5,000 U every 8 hours[c]
	Dalteparin	5,000 U once daily
	Enoxaparin	40 mg once daily
	Fondaparinux[d]	2.5 mg once daily
Surgical patients[b]	UFH	5,000 U 2-4 hours preoperatively and every 8 hours[c] thereafter[e]
	Dalteparin	2,500 U 2-4 hours preoperatively[e] and 5,000 U once daily thereafter[f]
		Or 5,000 U 2-4 hours preoperatively[e] or 10-12 hours preoperatively and 5,000 U once daily thereafter[f]
	Enoxaparin	40 mg 2-4 hours preoperatively[e] or 10-12 hours preoperatively and 40 mg once daily thereafter[f]
	Fondaparinux[d]	2.5 mg once daily beginning 6-8 hours postoperatively
Outpatients[b]	Dalteparin[d,g]	5,000 U once daily
	Enoxaparin[d,g]	40 mg once daily
	Fondaparinux[d,h]	2.5 mg once daily
	Apixaban[d]	2.5 mg orally twice daily
	Rivaroxaban[d]	10 mg orally once daily
Treatment of established VTE[i]		
Initial	UFH[j]	80 U/kg IV bolus, then 18 U/kg/h IV and adjust dose based on aPTT[k]
	Dalteparin[j,l,m]	100 U/kg every 12 hours
		200 U/kg once daily
	Enoxaparin[j,l,m,n]	1 mg/kg every 12 hours
		1.5 mg/kg once daily
	Tinzaparin[j,l,m,o]	175 U/kg once daily
	Fondaparinux[j,l,p]	< 50 kg: 5.0 mg once daily
		50-100 kg: 7.5 mg once daily
		> 100 kg: 10 mg once daily
	Rivaroxaban	15 mg orally every 12 hours for 21 days
Long term[p,q,r]	Dalteparin[l,m,s]	200 U/kg once daily for 1 month, then 150 U/kg once daily
	Enoxaparin[l,m,n]	1.5 mg/kg once daily
		1 mg/kg every 12 hours
	Tinzaparin[m,o]	175 U/kg once daily
	Warfarin	Adjust dose to maintain INR 2-3
	Rivaroxaban[m,t]	15 mg orally every 12 hours for 21 days, followed by 20 mg once daily thereafter (both doses with food)
	Edoxaban[m,t]	Needs at least 5 days of parenteral anticoagulation prior to its start, then switch to 60 mg orally once daily or 30 mg orally once daily in those weighing ≤ 60 kg, who have creatinine clearance between 30 and 50 mL/min, or who need concomitant use of a P-glycoprotein inhibitor

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; IV, intravenous; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a]All doses are given as subcutaneous injections except as indicated; renal and liver function as well as weight and potential drug-drug interactions must be taken into account when selecting agents and doses. Inducers or inhibitors of P-glycoprotein can interact with edoxaban, rivaroxaban, and apixaban. Inducers or inhibitors of CYP3A4 can interact with rivaroxaban and apixaban.[74,75] Please see the US Food and Drug Administration package inserts for further dosing information, including renal or liver function dose adjustment needs.

[b]Duration for medical patients is for the length of hospital stay or until fully ambulatory. For surgical patients, prophylaxis should be continued for at least 7-10 days. Extended prophylaxis for up to 4 weeks should be considered for high-risk patients. Duration for outpatient prophylaxis is somewhat uncertain, as most studies did not assess beyond 6 months.

[c]UFH 5,000 U every 12 hours has also been used in moderate-risk cancer but appears to be less effective, particularly in oncologic surgery.

[d]This drug is not approved by the US Food and Drug Administration for this indication.

[e]UFH: The first prophylactic UFH dose should be administered no sooner than 1 hour after needle/catheter placement. In patients receiving preoperative prophylactic low-dose UFH, neuraxial puncture/catheter manipulation or removal should not occur within the first 4-6 hours after UFH administration. Subsequent UFH administration may occur no earlier than 1 hour after catheter removal. In patients receiving preoperative therapeutic UFH (> 15,000 U/24 hours), neuraxial block/catheter removal or manipulation should not occur within 12 hours after UFH administration.

Low-molecular-weight heparin (LMWH): The first prophylactic LMWH dose should be administered no sooner than 4 hours after needle/catheter placement. In patients receiving preoperative prophylactic LMWH doses, neuraxial puncture/catheter manipulation or removal should not occur within the first 12 hours after LMWH administration. Subsequent LMWH administration may occur no earlier than 4 hour after catheter removal. In patients receiving preoperative therapeutic LMWH doses, neuraxial block/catheter removal or manipulation should not occur within 24 hours after heparin administration.

Clinicians should refer to their institutional guidelines and/or the American Society of Regional Anesthesia Guidelines for more detailed information about LMWH and other agents.[135]

[f]Clinicians should follow the regimens for the initiation and dosing of preoperative LMWH approved by regulatory agencies, as shown in the package insert.

[g]Higher prophylactic doses were used for patients with pancreatic cancer: dalteparin 200 IU/kg once daily for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks in FRAGEM[70] and enoxaparin 1 mg/kg once daily in CONKO-004.[71]

[h]Fondaparinux has not been studied in the outpatient prophylaxis setting. It should only be considered if the patient has contraindications for other LMWH and direct oral anticoagulant (DOAC) use is considered an inferior option.

[i]Contraindications to therapeutic anticoagulation are listed in Table 2.

[j]Parenteral anticoagulants should overlap with warfarin for 5-7 days minimum and should be continued until the INR is in the therapeutic range for 2 consecutive days.

[k]UFH infusion rate should be adjusted to maintain the aPTT within the therapeutic range in accordance with local protocols to correspond with a heparin level of 0.3-0.7 U/mL using a chromogenic antifactor Xa assay.

[l]Dependent on significant renal clearance; avoid in patients with creatinine clearance ≤ 30 mL/min or adjust dose based on antifactor Xa levels.

[m]Optimal dose unclear in patients > 120 kg.

[n]Twice-daily dosing may be more efficacious than once-daily dosing for enoxaparin based on post hoc data.

[o]This drug is not available in the United States.

[p]Fondaparinux had a higher rate of recurrent thrombosis and no difference in bleeding compared with enoxaparin in patients with cancer in a post hoc subgroup analysis.[153] It is not a standard option but may be used for long-term anticoagulation if standard LMWH or DOACs are not a feasible option for the patient. Dosing for long-term treatment with fondaparinux is the same as for initial treatment (fondaparinux prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021345s035lbl.pdf).

[q]Total duration of therapy depends on clinical circumstances. See text for more detailed discussion.

[r]Apixaban and dabigatran do not have fully published results from cancer-specific clinical trials. Prospective randomized trial data in patients with cancer with active disease on cancer therapy are needed prior to their use. Therefore, they are currently not recommended for routine use in patients with cancer with active disease.

[s]This is the only LMWH with US Food and Drug Administration approval for extended therapy to prevent recurrent thrombosis in patients with cancer.

[t]Edoxaban has the highest level of evidence for patients with cancer among all the DOACs, followed by rivaroxaban. Limited data from small, unpublished patient series suggest that the efficacy of DOACs in patients with a weight > 120 kg might be reasonable based on anti-Xa levels. The data are very limited, however, and LMWH is likely still preferred in this setting. Please refer to the package inserts for detailed information regarding potential dosing adjustment needs, especially regarding renal impairment, liver failure, weight extremes, or drug-drug interaction.

higher than the risk in white patients. The risk in Asian patients was similar to that of white patients.[145] Awareness of disparities in health and access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[146,147] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[148,149]

Discussion of cost can be an important part of shared decision making.[150] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease, and there are two or more treatment options that are comparable in terms of benefits and harms.[150]

Table 4 lists estimated prices for the available treatment options addressed in this guideline. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates. Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial

TABLE 4. Estimated Prices for Anticoagulants

Setting	Agent	Dose	Schedule	HCPCS Dosage	Medicare Payment Limit (US$)	Price Per Dose (US$)	Price Per Day (US$)
Pharmacologic (anticoagulant) prophylaxis							
Hospitalized medical patients	Unfractionated heparin	5,000 U	Every 8 hours	1,000 U	0.199	1.00	2.99
	Dalteparin	5,000 U	Once daily	2,500 U	14.982	29.96	29.96
	Enoxaparin	40 mg	Once daily	10 mg	0.872	3.49	3.49
	Fondaparinux	2.5 mg	Once daily	0.5 mg	2.283	11.42	11.42
Surgical patients	Unfractionated heparin	5,000 U	2-4 hours preoperatively and every 8 hours thereafter	1,000 U	0.199	1.00	2.99 (postoperatively)
	Dalteparin	2,500 U	2-4 hours preoperatively and 5,000 U once daily thereafter	2,500 U	14.982	14.98	29.96 (postoperatively)
		or					
		5,000 U	2-4 hours or 10-12 hours preoperatively and 5,000 U once daily thereafter				
	Enoxaparin	40 mg	2-4 hours or 10-12 hours preoperatively and once daily thereafter	10 mg	0.872	3.49	3.49 (postoperatively)
	Fondaparinux	2.5 mg	Once daily beginning 6-8 hours postoperatively	0.5 mg	2.283	11.42	11.42
Outpatients	Dalteparin	5,000 U	Once daily	2,500 U	14.982	29.96	29.96
	Enoxaparin	40 mg	Once daily	10 mg	0.872	3.49	3.49
	Fondaparinux	2.5 mg	Once daily	0.5 mg	2.283	11.42	11.42
	Apixaban	2.5 mg	Twice daily	NA	NA	7.78	15.56
	Rivaroxaban	10 mg	Once daily	NA	NA	15.69	15.69
Treatment of established VTE							
Initial	Unfractionated heparin	80 U/kg IV, then 18 U/kg IV	Bolus (80 U/kg) then per hour (18 U/kg); adjust dose based on aPTT	1,000 U	0.199	80 U/kg: 1.12* 18 U/kg: 0.25*	0.25/hour* (after initial bolus)
	Dalteparin	100 U/kg	Every 12 hours	2,500 U	14.982	41.95*	83.90*
		or					
		200 U/kg	Once daily				
	Enoxaparin	1 mg/kg	Every 12 hours	10 mg	0.872	6.10*	12.21*
		or					
		1.5 mg/kg	Once daily			9.16*	9.16*
	Fondaparinux	< 50 kg: 5.0 mg	Once daily	0.5 mg	2.283	22.83	22.83
		50-100 kg: 7.5 mg	Once daily	0.5 mg	2.283	34.25	34.25
		> 100 kg: 10 mg	Once daily	0.5 mg	2.283	45.66	45.66
	Rivaroxaban	15 mg	Every 12 hours	NA	NA	15.69	31.38

(continued on following page)

TABLE 4. Estimated Prices for Anticoagulants (continued)

Setting	Agent	Dose	Schedule	HCPCS Dosage	Medicare Payment Limit (US$)	Price Per Dose (US$)	Price Per Day (US$)
Long term	Dalteparin	200 U/kg	Once daily for 1 month	2,500 U	14.982	83.90*	83.90*
		then					
		150 U/kg	Once daily			62.92*	62.92*
	Enoxaparin	1 mg/kg	Every 12 hours	10 mg	0.872	6.10*	12.21*
		or					
		1.5 mg/kg	Once daily			9.16*	9.16*
	Rivaroxaban	15 mg	Every 12 hours for 21 days	NA	NA	15.69	31.38
		then					
		20 mg	Once daily			15.69	15.69
	Edoxaban	60 mg	Once daily	NA	NA	14.56	14.56

NOTE. Drug prices were estimated from a third-party payer perspective, based on reimbursement rates from the Centers for Medicare & Medicaid Services that are widely accepted by providers, computed at the manufacturer's average sales price. Other treatment-related direct and indirect costs were not considered. Actual treatment costs and reimbursement will vary considerably across regions, payers, institutions, and practices as well as over time, and readers should consult current local cost information specific to their practice setting. Prices per dose were for a single infusion or per pill for orally administered medications. Prices were based on Medicare Part B payment allowance limits effective July 1, 2018 (with no administration fees or other adjustments).[154] Prices for orally administered drugs reimbursed through Medicare Part D were identified in the Plan Finder for a beneficiary living within zip code 10065.[155] To remain as consistent as possible with prior methodology, we selected a Humana prescription drug plan with the lowest cost for beneficiaries to identify the full cost of each drug.[86] Of note, drug prices are dynamic, and the prices listed in the table may not reflect current prices.

Abbreviations: aPTT, activated partial thromboplastin time; HCPCS, Healthcare Common Procedure Coding System; IV, intravenous; NA, not applicable; US$, US dollars; VTE, venous thromboembolism.

*Based on a 70-kg adult.

counseling services available to address this complex and heterogeneous landscape.[150]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from August 15, 2018, through August 29, 2018, and from April 29, 2019, through May 13, 2019. The second round of public comment was prompted by revisions made in response to the AVERT[36] and CASSINI[44] trials, which were published in late 2018 and early 2019, respectively. Response categories of "Agree as written"; "Agree with suggested modifications"; and "Disagree. See comments" were captured for every proposed recommendation. Of the five respondents, three agreed with the recommendations as written, and two provided comments that were reviewed before finalizing the guideline. The guideline was also reviewed in full by two external reviewers.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Practice[151] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[137] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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N.S.K. and A.F. were Expert Panel Co-Chairs.

Editor's Note

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01461.

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ACKNOWLEDGMENT

The Expert Panel thanks William Tew, MD, Tracey Weisberg, MD, Marc Carrier, MD, Jeffrey Zwicker, MD, and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this guideline. Special thanks to Gary H. Lyman, MD, MPH, who served as Expert Panel Co-Chair from December 2017 to February 2019. Thanks also to Nicole M. Kuderer, MD, and Alok A. Khorana, MD, for serving on the writing group.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update Expert Panel Membership

Name and designation	Affiliation/Institution	Role/Area of Expertise
Anna Falanga, MD (co-chair)	Hospital Papa Giovanni XXIII, Bergamo; and University of Milan Bicocca, Milan, Italy	Hematology
Nigel S. Key, MB ChB (co-chair)	University of North Carolina, Chapel Hill, NC	Hematology
Gary H. Lyman, MD, MPH	Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA	Health outcomes research/evidence-based medicine methodology
		Hematology and medical oncology
Alok A. Khorana, MD	Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH	Hematology and medical oncology
Nicole M. Kuderer, MD	Advanced Cancer Research Group and University of Washington, Seattle, WA	Health outcomes research/evidence-based medicine methodology
		Hematology and medical oncology
Agnes Y.Y. Lee, MD, MSc	University of British Columbia, BC Cancer Agency, Vancouver, British Columbia, Canada	Hematology
Juan I. Arcelus, MD, PhD	Hospital Universitario Virgen de las Nieves, University of Granada, Granada, Spain	Surgery
Edward P. Balaban, DO, PGIN representative	Penn State Cancer Institute, Hershey, PA	Hematology and medical oncology
Christopher R. Flowers, MD, MS	Winship Cancer Institute, Emory University, Atlanta, GA	Hematology and medical oncology
Charles W. Francis, MD	James P Wilmot Cancer Center and Department of Medicine, University of Rochester, Rochester, NY	Hematology and medical oncology
Leigh E. Gates, BA, CPHQ	Denver, CO	Patient representative
Ajay K. Kakkar, MD, PhD	Thrombosis Research Institute and University College, London, London, United Kingdom	Surgery
Mark N. Levine, MD, MSc	McMaster University, Hamilton, Ontario, Canada	Hematology and medical oncology
Howard A. Liebman, MA, MD	Keck School of Medicine, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA	Hematology and medical oncology
Margaret A. Tempero, MD	University of California, San Francisco, Pancreas Center, San Francisco, CA	Hematology and medical oncology
Sandra L. Wong, MD, MS	Dartmouth-Hitchcock Medical Center, Lebanon, NH	Surgical oncology
Kari Bohlke, ScD	American Society of Clinical Oncology, Alexandria, VA	ASCO practice guidelines staff (health research methods)

Abbreviations: CPHQ, Certified Professional in Healthcare Quality; PGIN, Practice Guideline Implementation Network.