ASCO special articles

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

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abstract

PURPOSE To conduct an update of the ASCO venous thromboembolism (VTE) guideline.

METHODS After publication of potentially practice-changing clinical trials, identified through ASCO's signals approach to updating, an updated systematic review was performed for two guideline questions: perioperative thromboprophylaxis and treatment of VTE. PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) published between November 1, 2018, and June 6, 2022.

RESULTS Five RCTs provided information that contributed to changes to the 2019 recommendations. Two RCTs addressed direct factor Xa inhibitors (either rivaroxaban or apixaban) for extended thromboprophylaxis after surgery. Each of these postoperative trials had important limitations but suggested that these two oral anticoagulants are safe and effective in the settings studied. An additional three RCTs addressed apixaban in the setting of VTE treatment. Apixaban was effective in reducing the risk of recurrent VTE, with a low risk of major bleeding.

RECOMMENDATIONS Apixaban and rivaroxaban were added as options for extended pharmacologic thromboprophylaxis after cancer surgery, with a weak strength of recommendation. Apixaban was also added as an option for the treatment of VTE, with high quality of evidence and a strong recommendation.

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

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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] People 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]

ASCO first published a VTE guideline in 2007,[6] with updates in 2013,[7] 2014,[8] and 2019.[9] Pending a full update of the 2019 guideline, the current update adds apixaban as an option for the treatment of VTE in patients with cancer and addresses recent evidence regarding direct factor Xa inhibitors for extended postoperative thromboprophylaxis. These topics were identified using ASCO's signals approach to guideline updating, which allows for an expedited response to important, recommendation-altering evidence.[10] The term direct factor Xa inhibitors is used in this update rather than the previously used direct oral anticoagulants for increased specificity.

GUIDELINE QUESTIONS

This clinical practice guideline focuses on two of the six clinical questions from the 2019 guideline: Clinical Question 3: Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis, and Clinical Question 4: What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

METHODS

Guideline Development Process

This systematic review-based guideline update 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). One full panel meeting was held, and members were

ASSOCIATED CONTENT

Appendix

Data Supplement

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

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THE BOTTOM LINE

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

Guideline Question

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

Target Population

Adults with cancer.

Target Audience

Clinicians who provide care to adults with cancer (physicians, nurses, advanced practice providers, oncology pharmacists, and others), adults with cancer, and family members and caregivers.

Methods

An Expert Panel was convened for an update of recommendations on the basis of a systematic review of the medical literature.

Updated Recommendations

See Table 1 for the full list of recommendations.

Clinical question 3: Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

Recommendation 3.7. Patients who are candidates for extended pharmacologic thromboprophylaxis after surgery may be offered prophylactic doses of low molecular weight heparin (LMWH) (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong). Alternatively, patients may be offered prophylactic doses of rivaroxaban or apixaban after an initial period of LMWH or unfractionated heparin (UFH) (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement. Evidence for rivaroxaban and apixaban in this setting remains limited. The two available trials differed with respect to type of cancer, type of surgery, and timing of rivaroxaban or apixaban initiation after surgery.

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, rivaroxaban, or apixaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5-10 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, rivaroxaban, or apixaban for at least 6 months are preferred over vitamin K antagonists (VKAs) because of improved efficacy. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible. There is reduction in recurrent thrombosis but an increase in clinically relevant nonmajor bleeding risk with direct factor Xa inhibitors compared with LMWH. Caution with direct factor Xa inhibitors is warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked before using a direct factor Xa inhibitor (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

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.

asked to provide ongoing input on the quality and assessment of the evidence, generation of recommendations, draft content, and review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the expert panel co-chairs and corresponded with the panel via e-mail to coordinate the process to completion. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These 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 the *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 Evidence Based Medicine Committee (EBMC) before publication. All funding for the administration of the project was provided by ASCO.

ASCO uses a signals approach to facilitate guideline updating.[10] This approach is intended to identify new, potentially practice-changing data (ie, signals) that might translate into revised practice recommendations. The approach relies on routine literature searching and the expertise of ASCO guideline panel members to identify signals. The ASCO Guideline Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information.

For this update, the signals were a randomized controlled trial (RCT) assessing apixaban for VTE treatment in patients with cancer (the CARAVAGGIO trial[11]), as well as RCTs evaluating direct factor Xa inhibitors for extended postoperative thromboprophylaxis.[11,12] Apixaban was not listed as an option for VTE treatment in the 2019 guideline, nor were direct factor Xa inhibitors listed as options for perioperative thromboprophylaxis.

A systematic review of these topics (treatment of VTE and perioperative thromboprophylaxis) was conducted and involved online searches of PubMed and the Cochrane library for RCTs published between November 1, 2018, and June 6, 2022. Articles were selected for inclusion in the systematic review on the basis of the following criteria.

- Population: Adults with cancer
- Interventions: Pharmacologic agents used for VTE treatment or for perioperative thromboprophylaxis
- Comparisons: Placebo or usual care
- Outcomes: VTE, major bleeding
- Sample size: ≥50

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, and narrative reviews; (3) published in a non-English language.

The guideline recommendations were crafted, in part, using the *Guidelines Into Decision Support* methodology.[14] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice.

Ratings for evidence quality and type and strength of the recommendation are provided with each recommendation. For consistency with the previous version of the guideline, the same rating system was used, with definitions provided in Appendix Table A2. Evidence quality was rated as high, intermediate, low, or insufficient. Strength of the recommendation was classified as strong, moderate, or weak. The quality of included RCTs was assessed on the basis of factors such as blinding, adequate random assignment, sufficient sample size, intention-to-treat analyses, and funding sources.

The ASCO Expert Panel and guidelines staff work with cochairs to keep abreast of any additional substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO determines the need to update.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied on as being complete or accurate nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words such as must, must not, should, and should not indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an as is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

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/guideline-methodology). 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, and other intellectual property; expert testimony; travel, accommodations, and 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 literature search identified 176 publications. For the question on perioperative thromboprophylaxis, the search identified eight eligible RCTs. Five of the eight[13-17] assessed low molecular weight heparin (LMWH) and did not alter recommendations from the 2019 guideline.[9] The remaining three trials assessed a direct factor Xa inhibitor either during hospitalization[18] or for extended postoperative thromboprophylaxis.[11,12] The trial during hospitalization involved 94 patients undergoing surgery for glioma, who received rivaroxaban or placebo from admission to discharge.[18] The evidence from a single study in this setting was not deemed adequate for a change in recommendations. The two larger studies of extended postoperative thromboprophylaxis are discussed in detail in the Recommendations section.[11,12]

Five eligible RCTs addressed VTE treatment. Two of the five[19,20] assessed rivaroxaban and did not alter recommendations from the 2019 guideline, which listed rivaroxaban as an option for VTE treatment. The remaining three RCTs assessed apixaban and are discussed in detail in the Recommendations section.[21-23]

Evidence tables are provided in the Data Supplement (online only). Evidence supporting unchanged recommendations is reviewed in previous versions of this guideline.[6-9]

Evidence Quality Assessment

The overall quality of evidence for the safety and efficacy of direct factor Xa inhibitors for extended postoperative thromboprophylaxis was low. The two included studies each had sample size limitations and differed with respect to patient population and timing of the intervention. Overall quality of evidence was high for prevention of recurrent VTE and avoidance of major bleeding in studies that compared apixaban with LMWH for the treatment of VTE. Quality results for the included RCTs are provided in the Data Supplement.

UPDATED RECOMMENDATIONS

Clinical Question 3

Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

The full set of perioperative recommendations is provided in Table 1. For clarity, one of the recommendations from the 2019 guideline (Recommendation 3.5) was split into three separate recommendations in this update (Recommendations 3.5-3.7). Recommendation 3.7 contains new information about the options that may be offered for extended postoperative thromboprophylaxis. The population of patients to whom this applies is described in Recommendation 3.6 (Table 1).

Recommendation 3.7. Patients who are candidates for extended pharmacologic thromboprophylaxis after surgery may be offered prophylactic doses of LMWH (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong). Alternatively, patients may be offered prophylactic doses of rivaroxaban or apixaban after an initial period of LMWH or unfractionated heparin (UFH) (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement. Evidence for rivaroxaban and apixaban in this setting remains limited. The two available trials differed with respect to type of cancer, type of surgery, and timing of rivaroxaban or apixaban initiation after surgery.

Literature review update and analysis. Two RCTs addressed direct factor Xa inhibitors for extended postoperative thromboprophylaxis.[11,12] The double-blind PROLAPS-II trial compared rivaroxaban with placebo in 582 patients undergoing laparoscopic surgery for colorectal cancer.[11] Exclusion criteria included an increased risk of bleeding (eg, known brain metastases), other indications for anticoagulant therapy, renal insufficiency, and liver failure. Study treatment began 7 days (±2 days) after surgery and continued for 3 weeks. From the time of surgery to the start of study treatment, all patients received LMWH. Trial enrollment ended early, after inclusion of 582 of the planned 646 patients, because of study drug expiration. The primary outcome (a composite of symptomatic VTE, asymptomatic DVT, or VTE-related death in the first 28 days after surgery), occurred in 1% of patients in the rivaroxaban arm and 3.9% of patients in the placebo arm ($P = .03$). Major bleeding occurred in 0.7% of patients in the rivaroxaban arm and zero patients in the placebo arm.

Postoperative thromboprophylaxis with apixaban versus enoxaparin was evaluated in a randomized, open-label trial of 400 patients undergoing surgery for suspected or confirmed gynecologic cancer.[12] Ultimately, 19.6% of patients in the apixaban arm and 18.8% of patients in the enoxaparin arm did not have cancer. Exclusion criteria included history of VTE, long-term use of nonsteroidal anti-inflammatory drugs, concurrent use of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, history of severe renal or hepatic disease, or history of conditions related to abnormal bleeding or hypercoagulability. Patients received heparin on the first postoperative day, with random assignment to apixaban or enoxaparin within the first week after

TABLE 1. VTE Recommendations

Clinical Question	Recommendations	Type; Evidence Quality; Strength of Recommendation
1. Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?	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
	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
	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
2. Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?	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
	2.2. High-risk outpatients with cancer (Khorana score of 2 or higher before starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or 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
	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
3. Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?	3.1. All patients with malignant disease undergoing major surgical intervention should be offered pharmacologic thromboprophylaxis with either UFH or LMWH unless contraindicated because of active bleeding, high bleeding risk, or other contraindications	Type: Evidence based Evidence quality: High Strength of recommendation: Strong
	3.2. Prophylaxis with UFH or LMWH should be commenced preoperatively	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Moderate
	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
	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
	3.5. Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7-10 days	Type: Evidence based Evidence quality: High Strength of recommendation: Moderate to Strong
	3.6. Extended pharmacologic thromboprophylaxis for up to 4 weeks postoperatively should be offered to 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
	3.7. **(Updated)** Patients who are candidates for extended pharmacologic thromboprophylaxis after surgery may be offered prophylactic doses of LMWH	Type: Evidence based Evidence quality: High Strength of recommendation: Strong
	Alternatively, patients may be offered prophylactic doses of rivaroxaban or apixaban after an initial period of LMWH or UFH	Type: Evidence based Evidence quality: Low Strength of recommendation: Weak
	Qualifying statement: *Evidence for rivaroxaban and apixaban in this setting remains limited. The two available trials differed with respect to type of cancer, type of surgery, and timing of rivaroxaban or apixaban initiation after surgery*	

(continued on following page)

TABLE 1. VTE Recommendations (continued)

Clinical Question	Recommendations	Type; Evidence Quality; Strength of Recommendation
4. What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?	4.1. **(Updated)** Initial anticoagulation may involve LMWH, UFH, fondaparinux, rivaroxaban, or apixaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5-10 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
	4.2. **(Updated)** For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over VKAs because of improved efficacy. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible. There is reduction in recurrent thrombosis but an increase in clinically relevant nonmajor bleeding risk with direct factor Xa inhibitors compared with LMWH. Caution with direct factor Xa inhibitors is warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked before using a direct factor Xa inhibitor	Type: Evidence based Evidence quality: High Strength of recommendation: Strong
	4.3. Anticoagulation with LMWH, direct factor Xa inhibitors, 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
	4.4. On the basis of 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 because of 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
	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
	4.6. For patients with primary or metastatic central nervous system 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 Evidence quality: Low Strength of recommendation: Moderate
	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
	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
5. Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?	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
6. What is known about risk prediction and awareness of VTE among patients with cancer?	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 on the basis of a validated risk assessment tool (Khorana score)	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Strong
	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

NOTE. Notes regarding off-label use in guideline recommendations: LMWH and direct factor Xa inhibitors have not been FDA approved for thromboprophylaxis in outpatients with cancer. Outside of LMWH approval for thromboprophylaxis in patients undergoing abdominal surgery, anticoagulants have not been FDA approved for thromboprophylaxis in patients undergoing cancer surgery. Dalteparin is the only LMWH with FDA approval for extended therapy to prevent recurrent venous thromboembolism in patients with cancer.

Abbreviations: DVT, deep vein thrombosis; FDA, US Food and Drug Administration; LMWH, low molecular weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

surgery, when deemed safe by the operating surgeon. Study treatment was provided for 28 days, and patients were followed for a total of 90 days. Major bleeding occurred in one patient in each study arm. Clinically relevant nonmajor bleeding occurred in 5.4% of patients in the apixaban arm and 9.7% of patients in the enoxaparin arm ($P = .11$). VTE, a secondary outcome, occurred in 1% of patients in the apixaban arm and 1.5% of patients in the enoxaparin arm ($P = .68$). Although patient satisfaction with ease of taking the medication was significantly higher in the apixaban group compared with enoxaparin, it is interesting to note that the adherence to the prophylactic regimen was similar: 84.8% in the apixaban group and 83.7% in the enoxaparin group.

Clinical interpretation. Previously, the recommendation regarding VTE perioperative prophylaxis in patients with malignancies did not include direct oral anticoagulants, given the lack of data in this setting. However, in the past 2 years, two randomized clinical trials showed evidence for safety and efficacy of two factor Xa inhibitors for extended VTE prophylaxis, rivaroxaban after laparoscopy for colorectal cancer,[11] and apixaban after laparotomy or laparoscopy for gynecological cancer.[12] The panel evaluated these studies, and the revised version of the guidelines now includes a new (weak) recommendation on extended postoperative prophylaxis with apixaban or rivaroxaban, in addition to prophylactic dose LMWH, after cancer surgery for patients who are candidates for extended prophylaxis. The two studies differ in the design, type of surgery (laparoscopic or open), type of cancer (colorectal cancer or gynecological cancer), comparator (placebo or LMWH), and primary outcome. Additional data from randomized clinical trials are necessary to strengthen this recommendation.

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, rivaroxaban, or apixaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5-10 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, rivaroxaban, or apixaban for at least 6 months are preferred over vitamin K antagonists (VKAs) because of improved efficacy. VKAs may be used if LMWH or direct factor Xa inhibitors are not accessible. There is reduction in recurrent thrombosis but an increase in clinically relevant nonmajor bleeding risk with direct factor Xa inhibitors compared with LMWH. Caution with direct factor Xa inhibitors is warranted in GI and genitourinary malignancies and other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked before using a direct factor Xa inhibitor (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Additional recommendations regarding the treatment of VTE are provided in Table 1.

Literature review update and analysis. Three RCTs evaluated apixaban for VTE treatment in patients with cancer.[21-23] The CARAVAGGIO trial was an open-label, noninferiority trial that enrolled 1,170 patients with cancer and symptomatic or incidental acute proximal DVT or PE.[21] The trial excluded patients with basal cell or squamous cell skin cancers, primary brain tumors, known brain metastases, or acute leukemia. Patients were randomly assigned to 6 months of treatment with either apixaban or dalteparin. Apixaban was noninferior to dalteparin for the primary outcome of recurrent VTE during the 6-month trial period. Recurrent VTE occurred in 5.6% of patients in the apixaban arm and 7.9% of patients in the dalteparin arm ($P < .001$ for noninferiority and $P = .09$ for superiority). Major bleeding occurred in 3.8% of patients in the apixaban arm and 4.0% of patients in the dalteparin arm. Subsequent publications reported on patient subgroups defined by cancer type,[24,25] cancer treatment,[26] and incidental versus symptomatic VTE.[27] Subgroup results for the safety and efficacy of apixaban versus dalteparin were generally consistent with the primary study findings. In analyses that combined patients across treatment arms, some characteristics were associated with higher overall risk of VTE recurrence or major bleeding. Patients with incidental VTE had a numerically lower risk of recurrence than patients with symptomatic VTE (4.3% *v* 7.4%) and a numerically higher risk of major bleeding (5.2% *v* 3.6%).[27] With regard to cancer type, rates of recurrent VTE were highest in patients with gynecological cancer (10.9%), GI cancer (8.8%), genitourinary cancer (6.5%), and lung cancer (5.5%).[24] Rates of major bleeding were highest in patients with genitourinary cancer (7.2%) and GI cancer (4.8%).

Apixaban was also compared with dalteparin for VTE treatment in the ADAM VTE trial.[22] The open-label, randomized, superiority trial evaluated 287 patients with cancer-associated VTE. The primary outcome of major bleeding occurred in zero patients in the apixaban arm and 1.4% of patients in the dalteparin arm ($P = .14$). Recurrent VTE occurred in 0.7% of patients in the apixaban arm and 6.3% of patients in the dalteparin arm ($P = .03$).

A smaller trial compared apixaban with enoxaparin in patients with cancer and acute DVT.[23] The analysis included 100 of the 138 patients who had been randomly assigned to treatment, and risks of recurrent VTE and major bleeding did not differ significantly between study arms.

Clinical interpretation. At the time of the last guideline revision in 2019, the efficacy and safety of apixaban had not been evaluated in the treatment of cancer-associated thrombosis. In this revision, three randomized clinical trials were considered by the panel, which agreed that apixaban

can now be recommended as an alternative to the previous options. Apixaban is one of three direct inhibitors of factor Xa, but unlike rivaroxaban or edoxaban, it is administered twice daily. Currently, there are no studies that have directly compared direct oral anticoagulants on a head-to-head basis in this clinical setting.

EXTERNAL REVIEW AND OPEN COMMENT

The draft, revised recommendations were released to the public for open comment from November 7 to November 21, 2022. Response categories of Agree as written, Agree with suggested modifications, and Disagree. See comments were captured for every proposed recommendation with 25 written comments received. Across recommendations, between 96% and 100% of respondents either agreed as written or agreed with slight modifications. One respondent disagreed with one recommendation. In addition, two members of the ASCO Supportive Care Guideline Advisory Group reviewed the full guideline, with one providing suggested revisions. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before EBMC review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

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 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.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Care[28] (https://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[29] (https://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a 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.

EQUAL CONTRIBUTION

N.S.K and A.F. were expert panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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APPENDIX

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

Name	Affiliation or Institution	Role or Area of Expertise
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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)

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: (a) strong evidence for a true net effect (eg, benefits exceed harms); (b) consistent results, with no or minor exceptions; (c) minor or no concerns about study quality; and/or (d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: (a) good evidence for a true net effect (eg, benefits exceed harms); (b) consistent results with minor and/or few exceptions; (c) minor and/or few concerns about study quality; and/or (d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: (a) limited evidence for a true net effect (eg, benefits exceed harms); (b) consistent results, but with important exceptions; (c) concerns about study quality; and/or (d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation