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Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer

ASCO Guideline Update

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Background & Methodology

Introduction

- 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.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
 - a systematic literature review by ASCO guidelines staff
 - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
 - final guideline approval by ASCO EBMC
- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This clinical practice guideline focuses on two of the six clinical questions from the 2019 guideline:

3. Should patients with cancer undergoing surgery receive peri-operative VTE prophylaxis?
4. What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

Target Population and Audience

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

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Summary of Updated Recommendations

Summary of Updated 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 LMWH
- Alternatively, patients may be offered prophylactic doses of rivaroxaban or apixaban after an initial period of LMWH or unfractionated heparin (UFH).

Evidence-based	
Evidence Quality	Strength of Recommendation
High	Strong
Evidence Quality	Strength of Recommendation
Low	Weak

Summary of Updated Recommendations

Qualifying Statement for Recommendation 3.7

- 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.

Summary of Updated Recommendations

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 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).

Evidence-based	
Evidence Quality	Strength of Recommendation
High	Strong

Summary of Updated Recommendations

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 gastrointestinal and genitourinary malignancies, and other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a direct factor Xa inhibitor.

Evidence-based	
Evidence Quality	Strength of Recommendation
High	Strong

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Summary of Previous Recommendations

Summary of Previous Recommendations

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.

Evidence-based	
Evidence Quality	Strength of Recommendation
Intermediate	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.

Evidence-based	
Evidence Quality	Strength of Recommendation
Low	Moderate

Summary of Previous Recommendations

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.

Informal consensus

Evidence Quality	Strength of Recommendation
Insufficient	Moderate

Recommendation 2.1

- Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer.

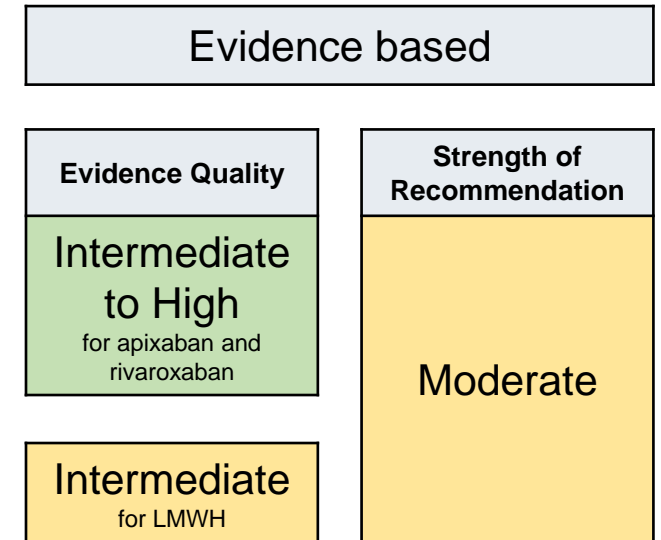
Evidence-based

Evidence Quality	Strength of Recommendation
Intermediate to High	Strong

Summary of Previous Recommendations

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 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.



Summary of Previous Recommendations

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.

Recommendation 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, or high bleeding risk, or other contraindications.

Informal consensus

Evidence Quality	Strength of Recommendation
Intermediate	Strong

Evidence-based

Evidence Quality	Strength of Recommendation
High	Strong

Summary of Previous Recommendations

Recommendation 3.2

- Prophylaxis with UFH or LMWH should be commenced preoperatively.

Informal consensus	
Evidence Quality	Strength of Recommendation
Intermediate	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.

Evidence-based	
Evidence Quality	Strength of Recommendation
Intermediate	Strong

Summary of Previous Recommendations

Recommendation 3.4

- A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients.

Evidence-based	
Evidence Quality	Strength of Recommendation
Intermediate	Moderate

Recommendation 3.5

- Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 to 10 days.

Evidence-based	
Evidence Quality	Strength of Recommendation
High	Moderate to Strong

Summary of Previous Recommendations

Recommendation 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.

Evidence-based	
Evidence Quality	Strength of Recommendation
High	Moderate to Strong

Summary of Previous Recommendations

Recommendation 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

Informal consensus	
Evidence Quality	Strength of Recommendation
Low	Weak to Moderate

Summary of Previous Recommendations

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 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.

Informal consensus	
Evidence Quality	Strength of Recommendation
Low to Intermediate	Moderate

Summary of Previous Recommendations

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.

Informal consensus	
Evidence Quality	Strength of Recommendation
Low to Intermediate	Weak

Summary of Previous Recommendations

Recommendation 4.6

- For patients with primary or metastatic central nervous system malignancies and established VTE, anti-coagulation 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.

Informal consensus

Evidence Quality
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.

Informal consensus

Evidence Quality
Low

Strength of Recommendation
Moderate

Summary of Previous Recommendations

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.

Informal consensus

Evidence Quality	Strength of Recommendation
Insufficient	Moderate

Recommendation 5

- Anticoagulant use is not recommended to improve survival in patients with cancer without VTE.

Evidence based

Evidence Quality	Strength of Recommendation
High	Strong

Summary of Previous Recommendations

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).

Evidence based	
Evidence Quality	Strength of Recommendation
Intermediate	Strong

Summary of Previous Recommendations

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.

Informal consensus	
Evidence Quality	Strength of Recommendation
Insufficient	Strong

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.

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Additional Information

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines
- Patient information is available at www.cancer.net

Guideline Panel Members

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Abbreviations

- ASCO, American Society of Clinical Oncology
- DVT, deep vein thrombosis
- EBMC, Evidence Based Medicine Committee
- LMWH, low molecular weight heparin
- min, minute
- mL, milliliter
- PE, pulmonary embolism
- UFH, unfractionated heparin
- VKAs, vitamin K antagonists
- VTE, venous thromboembolism

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