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ASCO SPECIAL ARTICLE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline Update provides recommendations with comprehensive discussion of the relevant literature for each recommendation. The Data Supplement, including evidence tables, is available at http://www.asco.org/guidelines/vte.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To provide recommendations about prophylaxis and treatment of venous thromboembolism (VTE) in patients with cancer. Prophylaxis in the outpatient, inpatient, and perioperative settings was considered, as were treatment and use of anticoagulation as a cancer-directed therapy.

Methods
A systematic review of the literature published from December 2007 to December 2012 was completed in MEDLINE and the Cochrane Collaboration Library. An Update Committee reviewed evidence to determine which recommendations required revision.

Results
Forty-two publications met eligibility criteria, including 16 systematic reviews and 24 randomized controlled trials.

Recommendations
Most hospitalized patients with cancer require thromboprophylaxis throughout hospitalization. Thromboprophylaxis is not routinely recommended for outpatients with cancer. It may be considered for selected high-risk patients. Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low–molecular weight heparin (LMWH) or low-dose aspirin. Patients undergoing major cancer surgery should receive prophylaxis, starting before surgery and continuing for at least 7 to 10 days. Extending prophylaxis up to 4 weeks should be considered in those with high-risk features. LMWH is recommended for the initial 5 to 10 days of treatment for deep vein thrombosis and pulmonary embolism as well as for long-term (6 months) secondary prophylaxis. Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE. Anticoagulation should not be used for cancer treatment in the absence of other indications. Patients with cancer should be periodically assessed for VTE risk. Oncology professionals should provide patient education about the signs and symptoms of VTE.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published an evidence-based clinical practice guideline on prophylaxis and treatment of venous thromboembolism (VTE) in 2007.[1] ASCO guidelines are updated at intervals determined by an Update Committee; this is a full guideline update. Table 1 provides a summary of the 2007 and 2012 guideline recommendations.

GUIDELINE 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?
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

Panel Composition

An Update Committee was formed (Appendix Table A1, online only) to review data published since the initial

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guideline and update recommendations, as warranted, considering evidence identified by the systematic review.

Guideline Development Process

The Update Committee met in July 2012 and had a second meeting via teleconference. During those meetings, the Update Committee reviewed evidence identified by the systematic review and revised guideline recommendations. Additional work on the guideline was completed electronically. The steering committee and lead ASCO staff person prepared an updated guideline to share with the Update Committee members for review. As per standard practice, the guideline was submitted to *Journal of Clinical Oncology* for review. The VTE Update Committee and the ASCO Clinical Practice Guideline Committee reviewed and approved this guideline document before publication.

Guideline Policy

The practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not recommend any particular product or course of medical treatment. Use of the practice guideline is voluntary. The Additional information is available at http://www.asco.org/guidelines/vte.

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.

Update Methodology

The goal of this update was to review evidence available since publication of the original guideline and to revise recommendations, as needed, about the prevention and treatment of VTE among patients with cancer. One new clinical question, regarding risk, was added, and a separate systematic review was completed to address this issue.

Literature Review and Analysis

Literature search strategy. The effectiveness search included the MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials databases. Conference proceedings from annual meetings of ASCO, the American Society of Hematology, the European Society of Medical Oncology, and the International Society of Thrombosis and Hemostasis were searched through 2012 or the most recent year available. The risk assessment search was completed in MEDLINE.

Reference lists from seminal articles, guidelines from other organizations, and recent review articles were hand searched for additional citations.

THE BOTTOM LINE

ASCO GUIDELINE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer

Interventions

- Pharmacologic anticoagulation

Target Audience

- Medical oncologists, surgical oncologists, hospitalists, oncology nurses

Key Recommendations

- Most hospitalized patients with cancer require thromboprophylaxis throughout hospitalization
- Thromboprophylaxis is not routinely recommended for ambulatory patients with cancer; it may be considered for very select high-risk patients
- Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low molecular–weight heparin (LMWH) or low-dose aspirin to prevent venous thromboembolism (VTE)
- Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days
- Extending postoperative prophylaxis up to 4 weeks should be considered in those with high-risk features
- LMWH is recommended for the initial 5 to 10 days of treatment for patients with established deep vein thrombosis and pulmonary embolism, as well as for long-term (6 months) secondary prophylaxis
- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE
- Anticoagulation should not be used to extend survival in patients with cancer in the absence of other indications
- Patients with cancer should be periodically assessed for VTE risk
- Oncology professionals should provide patient education about the signs and symptoms of VTE

Methods

- An Expert Panel was convened to develop clinical practice guideline recommendations based on a review of evidence provided by a systematic review of the medical literature

Additional Information

This guideline was published in *Journal of Clinical Oncology*. The Data Supplement, including evidence tables, and clinical tools and resources, can be found at www.asco.org/guidelines/vte.

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Table 1. VTE Prophylaxis and Treatment Recommendations

2013 Recommendation	Strength of Evidence Type and Strength of Recommendation	2007 Recommendation
Inpatients		
1.1 Hospitalized patients who have active malignancy with acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.	Evidence: strong Recommendation type, strength: evidence based, strong	Hospitalized patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications to anticoagulation.
1.2 Hospitalized patients who have active malignancy without additional risk factors may be considered for pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.	Evidence: moderate Recommendation type, strength: evidence based, strong	
1.3 Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion or in patients undergoing stem-cell/bone marrow transplantation.	Evidence: insufficient Recommendation type, strength: informal consensus, moderate	
Outpatients		
2.1 Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients.	Evidence: moderate Recommendation type, strength: evidence based, strong	Routine prophylaxis with an antithrombotic agent is not recommended.
2.2 Based on limited RCT data, clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy. Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms as well as dose and duration of prophylaxis in this setting.	Evidence: moderate Recommendation type, strength: evidence based, weak	
2.3 Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.	Evidence: moderate Recommendation type, strength: evidence based, strong	Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at high risk for thrombosis and warrant prophylaxis. Until such time as data are available from RCTs, LMWH or adjusted-dose warfarin (INR approximately 1.5) is recommended in patients with myeloma receiving thalidomide plus chemotherapy or dexamethasone. This recommendation is based on extrapolation from studies of postoperative prophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer. RCTs evaluating antithrombotic agents are needed in patients with multiple myeloma receiving thalidomide or lenalidomide plus chemotherapy and/or dexamethasone. Research identifying better markers of ambulatory patients with cancer most likely to develop VTE is urgently needed.
Perioperative		
3.1 All patients with malignant disease undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis with either UFH or LMWH unless contraindicated because of active bleeding or high bleeding risk.	Evidence: strong Recommendation type, strength: evidence-based, strong	All patients undergoing major surgical intervention for malignant disease should be considered for thromboprophylaxis. Patients undergoing laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes should receive pharmacologic thromboprophylaxis with either low-dose UFH or LMWH unless contraindicated because of high risk of bleeding or active bleeding.
3.2 Prophylaxis should be commenced preoperatively.	Evidence: moderate Recommendation type, strength: evidence based, moderate	Prophylaxis should be commenced preoperatively or as early as possible in the postoperative period.
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: moderate Recommendation type, strength: evidence based, strong	Mechanical methods may be added to pharmacologic methods but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because of active bleeding.
3.4 A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients.	Evidence: moderate Recommendation type, strength: informal consensus, moderate	A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients.
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 should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors as listed in Table 3. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis considering the individual patient.	Evidence: strong Recommendation type, strength: evidence based, strong to moderate	Prophylaxis should be continued for at least 7 to 10 days postoperatively. Prolonged prophylaxis for up to 4 weeks may be considered in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features such as residual malignant disease after operation, obese patients, and those with a history of VTE.

(continued on following page)

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Table 1. VTE Prophylaxis and Treatment Recommendations (continued)

2013 Recommendation	Strength of Evidence Type and Strength of Recommendation	2007 Recommendation
Treatment and secondary prophylaxis		
4.1 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).	Evidence: strong Recommendation type, strength: evidence based, strong	LMWH is the preferred approach for the initial 5 to 10 days of anticoagulant treatment of the patient with cancer with established VTE.
4.2 For long-term anticoagulation, LMWH for at least 6 months is preferred because of improved efficacy over VKAs. VKAs are an acceptable alternative for long-term therapy if LMWH is not available.	Evidence: strong Recommendation type, strength: evidence based, strong	LMWH given for at least 6 months is also the preferred approach for long-term anticoagulant therapy. VKAs with a targeted INR of 2 to 3 are acceptable for long-term therapy when LMWH is not available.
4.3 Anticoagulation with LMWH or VKA beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.	Evidence: insufficient Recommendation type, strength: informal consensus, weak to moderate	After 6 months, indefinite anticoagulant therapy should be considered for selected patients with active cancer, such as those with metastatic disease and those receiving chemotherapy. This recommendation is based on Panel consensus in the absence of clinical trials data.
4.4 The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy (see Table 4). It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal therapy with LMWH.	Evidence: weak to moderate Recommendation type, strength: informal consensus, moderate	The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy and in those with recurrent VTE despite adequate long-term therapy with LMWH.
4.5 For patients with primary CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications.	Evidence: moderate Recommendation type, strength: informal consensus, strong	For patients with CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications. Anticoagulation should be avoided in the presence of active intracranial bleeding, recent surgery, preexisting bleeding diathesis such as thrombocytopenia (platelet count < 50,000/μL), or coagulopathy.
4.6 Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time.	Evidence: insufficient Recommendation type, strength: informal consensus, strong	
4.7 Based on consensus, incidental PE and DVT should be treated in the same manner as symptomatic VTE. Treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.	Evidence: insufficient Recommendation type, strength: informal consensus, moderate	
Anticoagulation and survival		
5.1 Anticoagulants are not recommended to improve survival in patients with cancer without VTE.	Evidence: weak to moderate Recommendation type, strength: informal consensus, moderate	Anticoagulants are not recommended to improve survival in patients with cancer without VTE. Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.
5.2 Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.		
Risk assessment		
6.1 Based on consensus, the Panel recommends that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. Individual risk factors, including biomarkers or cancer site, do not reliably identify patients with cancer at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool (Table 5).	Evidence: moderate Recommendation type, strength: informal consensus, strong	New for 2012 Update
6.2 Based on consensus, the Panel recommends that oncologists educate patients regarding VTE, particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy.	Evidence: insufficient Recommendation type, strength: informal consensus, strong	

Abbreviations: INR, international normalized ratio; LMWH, low–molecular weight heparin; PE, pulmonary embolism; RCT, randomized controlled trial; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

The Update Committee reviewed the list of included reports for completeness. Subject headings and keywords used in the efficacy literature search included four major categories: VTE, anticoagulation, malignancy, and randomized controlled trials (RCTs). The full search string is available in the Data Supplement. The risk literature search also included four major categories: risk assessment, VTE, cancer, and cohort studies.

Inclusion and exclusion criteria. Articles for the efficacy systematic review were selected for inclusion if they were RCTs or systematic reviews of RCTs that assessed the efficacy and safety of anticoagulation in patients with cancer and included at least 50 patients per arm. Only data from conference proceedings available as full presentations or posters were included.

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For the risk systematic review, studies from the ambulatory setting that either developed or validated risk models were included. Only reports that included multivariate analyses were eligible. Risk assessment models limited to single cancer types were excluded.

Data extraction. Eligible reports for both reviews were preliminarily identified after the literature search. Full-text copies were obtained to further assess eligibility. Articles that met eligibility for the efficacy search underwent data extraction by ASCO staff for study design and quality, patient characteristics, outcomes, and adverse events. Outcomes of interest included symptomatic and asymptomatic thrombotic events found on screening, major and minor bleeding, early and overall mortality, sudden death, and adverse events. For the risk review, data extraction included study characteristics, quality, and risk assessment model development and evaluation. Outcomes of interest included factors incorporated into the risk assessment model, model equation, and outcomes according to risk.

Evidence summary tables (Data Supplement) were reviewed for accuracy and completeness by an ASCO staff member who was not involved in data extraction. Disagreements were resolved through discussion; the Steering Committee was consulted if necessary.

Study quality. Trial characteristics from the RCTs were extracted to evaluate the potential for bias. Study quality was also assessed for the reports in the risk systematic review.

Guideline and Conflicts of Interest

The Update Committee was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at http://www.asco.org/guidelinescoi). Members of the Update Committee completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

Revision Dates

At intervals, the Update Committee co-chairs and two Update Committee members designated by the co-chairs will determine the need for guideline revisions based on the available literature. If necessary, the Update Committee will be reconvened. When appropriate, the Update Committee will suggest revised recommendations to the Clinical Practice Guideline Committee.

RESULTS

Literature Search

The efficacy literature search yielded a total of 380 citations from MEDLINE, 531 citations from conference proceedings, and 18 from hand searching. Forty-two reports provisionally met inclusion and exclusion criteria and were selected for full-text review. Of those, reports from 30 trials and systematic reviews were selected for data extraction. The QUOROM diagram is available in the Data Supplement.

For the risk systematic review, the MEDLINE literature search yielded 664 citations. Of those, 54 provisionally met eligibility criteria and were selected for full-text review. Six articles were identified for data extraction.

Study Quality and Limitations of the Literature

Publications identified by the systematic review varied with respect to potential for bias, ranging from low to high. A majority of the trials were of moderate quality. Specific quality issues are discussed within the section for the relevant clinical question.

GUIDELINE RECOMMENDATIONS: CLINICAL QUESTION 1

Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

Recommendation 1.1

Hospitalized patients who have active malignancy with acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.

Recommendation 1.2

Hospitalized patients who have active malignancy without additional risk factors may be considered for pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.

Recommendation 1.3

Data are inadequate to support or oppose thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion or in patients undergoing stem-cell/bone marrow transplantation.

Literature Update and Analysis 1

Three randomized trials were identified by the systematic review: CERTIFY (Certoparin for Thromboprophylaxis in Medical Patients), CERTAIN (Certoparin Versus Unfractionated Heparin for the Prevention of Thromboembolic Complications in Acutely Ill Medical Patients), and EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients with Prolonged Immobilization).[2-4] EXCLAIM evaluated extended prophylaxis.[2] One systematic review and meta-analysis of inpatient thromboprophylaxis was also identified.[5] Dosing information is provided in Table 2.

Primary Prophylaxis

Both new primary prophylaxis trials in medically ill patients, CERTAIN and CERTIFY, compared a low molecular–weight heparin (LMWH), certoparin, with unfractionated heparin (UFH). The primary outcome for both trials was the composite of symptomatic or asymptomatic deep vein thrombosis (DVT), symptomatic pulmonary embolism (PE), or VTE-related death. Among the 172 patients randomly assigned in the CERTAIN trial, 8.0% and 9.2% in the UFH and LMWH groups, respectively, had active or previous cancer (not significant).[3] The primary end point was reported in 18% of patients receiving UFH and 10.7% of patients receiving certoparin (not significant).

Patients with cancer were eligible to participate in CERTIFY, but the percentage was not reported.[4] Among the 3,244 patients randomly assigned in this trial, the primary outcome of DVT or PE occurred in 3.9% in the certoparin arm compared with 4.5% receiving UFH (not significant). Both trials included an older patient population; the mean age in CERTIFY was > 78 years,[4] and in CERTAIN, it was > 70 years.[3] Neither trial reported data for cancer subgroups. Bleeding rates were higher with UFH compared with LMWH. Sudden death was not reported for either trial.

The systematic review examined pharmacologic thromboprophylaxis with LMWH, UFH, fondaparinux, and placebo.[5] DVT rates were lower with LMWH/fondaparinux compared with placebo (odds

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Table 2. Dosing Regimens for Prophylaxis/Treatment of VTE in Patients With Cancer

Drug	Regimen[a]
Pharmacologic (anticoagulant) prophylaxis	
Hospitalized medical patients[b]	
Unfractionated heparin	5,000 U once every 8 hours[c]
Dalteparin	5,000 U once daily
Enoxaparin	40 mg once daily
Fondaparinux[d]	2.5 mg once daily
Surgical patients[be]	
Unfractionated heparin	5,000 U 2-4 hours preoperatively and once every 8 hours[c] thereafter or 5,000 U 10-12 hours preoperatively and 5,000 U once daily thereafter
Dalteparin	2,500 U 2-4 hours preoperatively and 5,000 U once daily thereafter or 5,000 U 10-12 hours preoperatively and 5,000 U once daily thereafter
Enoxaparin	20 mg 2-4 hours preoperatively and 40 mg once daily thereafter or 40 mg 10-12 hours preoperatively and 40 mg once daily thereafter
Fondaparinux[d]	2.5 mg qd beginning 6-8 h postoperatively
Treatment of established VTE[f]	
Initial	
Unfractionated heparin[g]	80 U/kg IV bolus, then 18 U/kg per hour IV; adjust dose based on aPTT[h]
Dalteparin[gij]	100 U/kg once every 12 hours; 200 U/kg once daily
Enoxaparin[gijk]	1 mg/kg once every 12 hours; 1.5 mg/kg once daily
Tinzaparin[gijl]	175 U/kg once per day
Fondaparinux[gi]	< 50 kg, 5.0 mg once daily; 50-100 kg, 7.5 mg once daily; > 100 kg, 10 mg once daily
Long term[m]	
Dalteparin[jin]	200 U/kg once daily for 1 month, then 150 U/kg once daily
Enoxaparin[ijk]	1.5 mg/kg once daily; 1 mg/kg once every 12 hours
Tinzaparin[jl]	175 U/kg once daily
Warfarin	Adjust dose to maintain INR 2 to 3

Abbreviations: aPTT, activated partial thromboplastin time; FDA, US Food and Drug Administration; INR, international normalized ratio; IV, intravenous; LMWH, low–molecular weight heparin; VTE, venous thromboembolism.

[a]All doses are administered as subcutaneous injections except as indicated.

[b]Duration for medical patients is length of hospital stay or until fully ambulatory; for surgical patients, prophylaxis should be continued for at least 7 to 10 days. Extended prophylaxis for up to 4 weeks should be considered for high-risk patients.

[c]Unfractionated heparin 5,000 U every 12 hours has also been used but appears to be less effective.

[d]This drug is not approved by the FDA for this indication.

[e]When neuraxial anesthesia or analgesia is planned, prophylactic doses of once-daily LMWH should not be administered within 10 to 12 hours before the procedure/instrumentation (including epidural catheter removal). After the surgery, the first dose of LMWH can be administered 6 to 8 hours postoperatively. After catheter removal, the first dose of LMWH can be administered no earlier than 2 hours afterward. Clinicians should refer to their institutional guidelines and the American Society of Regional Anesthesia Guidelines for more information.[6]

[f]Contraindications to therapeutic anticoagulation are listed in Table 4.

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

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

[i]Dependent on significant renal clearance; avoid in patients with creatinine clearance ≤ 30 mL/minute or adjust dose based on anti–factor Xa levels.

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

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

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

[m]Total duration of therapy depends on clinical circumstances. See Clinical Question 4, section entitled "Initial and Long-Term Treatment Up to 6 Months," for more detailed discussion.

[n]This is the only LMWH with FDA approval for extended therapy to prevent recurrent thrombosis in patients with cancer.

ratio [OR], 0.60; 95% CI, 0.47 to 0.75) but similar between LMWH and UFH (OR, 0.92; 95% CI, 0.56 to 1.52). No differences in the rate of death or PE were noted between patients who were treated with LMWH/fondaparinux, UFH, or placebo. Major bleeding rates were similar across all treatment arms considered. Minor bleeding rates were similar with LMWH and UFH and greater than in placebo-treated patients. Cancer-specific rates were not provided for either VTE or bleeding.

Extended Prophylaxis

In an RCT, 6,085 acutely ill medical patients were assigned to extended prophylaxis with enoxaparin or placebo for 28 days (± 4 days) after receiving open-label enoxaparin for an initial 10 days (± 4 days).[2] Of the patients in the LMWH arm, 14.1% had cancer, as did 16.0% in the placebo arm. The primary outcomes were VTE defined as a composite of symptomatic or asymptomatic proximal DVT, symptomatic PE, and fatal PE, and major bleeding. The proportion of VTE events was greater with placebo: 4.0% versus 2.5% for an absolute risk difference of −1.53% (95% CI, −2.54% to −0.52%). Major bleeding was uncommon but significantly greater with active therapy: 0.8% versus 0.3%. The early mortality rate was similar across trial arms (hazard ratio [HR], 0.93; 95% CI, 0.65 to 1.32).[2] Cancer-specific data were not reported.

Trial Considerations

The inpatient trials enrolled mixed populations including patients with cancer as well as general medical patients. To date, no trials

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Table 3. Risk Factors and Biomarkers for Cancer-Associated Thrombosis

Cancer Related	Treatment Related	Patient Related	Biomarkers
Primary site	Chemotherapy	Older age	Platelet count (≥ 350,000/μL)
Stage (higher for advanced stage)	Antiangiogenic agents (eg, thalidomide, lenalidomide)	Race (higher in African Americans; lower in Asians/Pacific Islanders)	Leukocyte count (> 11,000/μL)
Cancer histology (higher for adenocarcinoma than squamous cell)	Hormonal therapy	Medical comorbidities (infection, renal disease, pulmonary disease, arterial thromboembolism)	Hemoglobin (< 10 g/dL)
Time after initial diagnosis (highest in first 3 to 6 months)	Erythropoiesis-stimulating agents	Obesity	
	Transfusions	History of VTE	
	Indwelling venous access devices	Diminished performance status	
	Radiation therapy	Inherited prothrombotic mutations	
	Surgery > 60 min		

Abbreviation: VTE, venous thromboembolism.

have evaluated inpatient thromboprophylaxis in a cancer-only population. These recommendations were formulated by extrapolating the best available data. All RCTs included reduced mobility as an eligibility criterion, but the definitions of immobility were not explicit or consistent. This limits generalizability of these data to all hospitalized patients with cancer and tempered the willingness of the Update Committee to recommend thromboprophylaxis for all inpatients with malignancy.

The extended thromboprophylaxis trial, CERTAIN, indicates that prolonging anticoagulation reduces VTE event rates but increases the risk of bleeding. Importantly, a midstudy amendment narrowed the eligible patient population after interim analysis noted limited efficacy in patients without reduced mobility.[2] Findings from this trial must be interpreted with this narrow patient population in mind.

Risk Among Inpatients

A vast majority of hospitalized patients with cancer are at moderate to high risk for thromboembolic events, because active cancer is a strong risk factor.[7-13] Most patients have additional risk factors, including comorbid conditions such as infection, immobility, or advanced age.[14] The benefit of prophylaxis increases with the risk of VTE. Table 3 includes a list of risk factors that can be used to evaluate risk in oncology inpatients. Risk is further addressed in Clinical Question 6.

CLINICAL QUESTION 2

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

Recommendation 2.1

Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients.

Recommendation 2.2

Based on limited RCT data, clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy. Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms as well as dose and duration of prophylaxis in this setting.

Recommendation 2.3

Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.

Literature Update and Analysis 2

The updated systematic review identified three systematic reviews[15-17] considering the ambulatory setting and nine RCTs.[18-25] Two RCTs, SAVE-ONCO (Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy),[18] and PROTECHT (Prophylaxis of Thromboembolism During Chemotherapy)[19] included patients with a variety of solid tumors. Two others, FRAGEM (Gemcitabine With or Without Dalteparin in Treating Patients With Locally Advanced or Metastatic Pancreatic Cancer)[21] and PROSPECT-CONKO 004 (Chemotherapy With or Without Enoxaparin in Pancreatic Cancer)[24,25] included only patients with pancreatic cancer. The PRODIGE (Dalteparin Low Molecular Weight Heparin for Primary Prophylaxis of Venous Thromboembolism in Brain Tumour Patients) trial examined anticoagulation for patients with glioma.[23] Two recent trials evaluated thromboprophylaxis in multiple myeloma.[20,22] Final publications of two trials discussed in the previous guideline are also discussed.[26]

Systematic Reviews

Two systematic reviews identified RCTs comparing LMWH prophylaxis in the outpatient setting with placebo or no prophylaxis. Estimated risk ratios (RRs) across trials indicated decreases in symptomatic VTE events with LMWH thromboprophylaxis of 0.53 (95% CI, 0.39 to 0.72) and 0.54 (95% CI, 0.31 to 0.95), respectively.[16,17] Neither meta-analysis noted a statistically significant increase in bleeding with LMWH. Of note, the second report included only trials of patients with advanced lung cancer from two RCTs.[16] The relative risk for symptomatic VTE was 0.58 (95% CI, 0.28 to 1.06).

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A recent Cochrane review compared the efficacy and safety of LMWHs, vitamin K antagonists (VKAs), and direct thrombin inhibitors with no intervention or placebo in ambulatory patients with cancer.[15] Fewer symptomatic VTEs occurred with LMWH thromboprophylaxis in the pooled analysis of > 2,400 patients (RR, 0.62; 95% CI, 0.41 to 0.99). Rates of major and minor bleeding were not consistently increased with anticoagulation compared with placebo. Four trials specifically considered the LMWH dalteparin, allowing a subgroup analysis of that agent. No difference in VTE event rates was noted between dalteparin and placebo (RR, 0.75; 95% CI, 0.42 to 1.32).

The absolute differences in symptomatic VTE event rates between treated and control patients were < 5% in most trials. Among the three systematic reviews, the absolute risk differences in VTE were 1.5%, 2.8%, and 1.7% with estimates of the number needed to treat (NNT) of 67, 36, and 59, respectively, to prevent one symptomatic VTE event across the included trials. Importantly, individual patient data were not evaluated, limiting the assessment of patients with different cancers, often receiving different cancer therapies and anticoagulants, and with varying degrees of VTE risk.

Recent Clinical Trials

Mixed solid tumors. The PROTECHT and SAVE-ONCO trials evaluated thromboprophylaxis in ambulatory patients with cancer receiving chemotherapy for locally advanced or metastatic solid tumors.[18,19] These double-blind trials compared anticoagulation with either the LMWH nadroparin or the ultra-LMWH semuloparin with placebo. Semuloparin is not available and has been withdrawn from marketing worldwide. The primary end point for PROTECHT was a composite of symptomatic VTEs and arterial thromboembolic events during treatment and follow-up.[19] In PROTECHT, 3.9% of patients in the control arm experienced events compared with 2.0% of patients treated with nadroparin for an NNT of 53 (one-tailed $P = .02$). Major bleeding rates were not different between the arms. In an exploratory subgroup analysis, thromboembolic event rates were greater in patients who received thromboprophylaxis compared with controls: 8.3% versus 5.9%. In SAVE-ONCO, fewer symptomatic VTE events occurred in patients who received semuloparin (1.2%) compared with placebo (3.4%; HR, 0.36; 95% CI, 0.21 to 0.60; $P < .001$).[18] The absolute risk difference for VTE events was 2.2% for an NNT of 45. Major bleeding was similar across arms (HR, 1.05; 95% CI, 0.55 to 1.99).

Two double-blind RCTs of ambulatory patients with metastatic breast carcinoma (TOPIC-1) or stage III/IV non–small-cell lung carcinoma (TOPIC-2) compared certoparin 3,000 IU subcutaneously once daily with placebo for 6 months.[26] The primary outcome was symptomatic or asymptomatic VTE. TOPIC-1 randomly assigned 353 patients but was stopped after an interim analysis revealed no difference between treatment arms. VTE occurred in 4% from both study arms, resulting in an OR of 1.02 (95% CI, 0.30 to 3.48). TOPIC-2 randomly assigned 547 patients, 4.5% of whom experienced VTE in the certoparin arm and 8.3% in the placebo arm (OR, 0.52; 95% CI, 0.23 to 1.12). Major bleeding in the certoparin and control arms was 1.7% and 0% in TOPIC-1 and 3.7% and 2.2% in TOPIC-2, respectively, neither of which was statistically significant. A post hoc exploratory analysis demonstrated a reduction in VTE in stage IV lung carcinoma in the certoparin arm (3.5% *v* 10.2%; $P = .032$).

Pancreatic cancer. The FRAGEM and PROSPECT-CONKO 004 trials enrolled patients with advanced pancreatic neoplasms.[21,25] The FRAGEM trial was a phase IIb RCT of 123 patients with advanced pancreatic cancer receiving gemcitabine-based chemotherapy comparing thromboprophylaxis with therapeutic doses of dalteparin up to 12 weeks, following a schedule similar to that of the CLOT (Randomized Comparison of Low Molecular–Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) trial, with no thromboprophylaxis.[21] VTE over the course of the study was reduced from 28% to 12%, with a relative risk of 0.42 (95% CI, 0.19 to 0.94; $P = .039$). No differences in rates of major bleeding or mortality between study arms were observed.

The PROSPECT-CONKO 004 trial was presented as an oral presentation but has not yet been published.[25] In this trial, 312 patients with stage IV pancreatic cancer being treated with gemcitabine-based chemotherapy were randomly assigned to enoxaparin at half the therapeutic dose for 3 months or no thromboprophylaxis. VTE was reduced from 15% to 5%, with a relative risk of 0.35 (95% CI, 0.16 to 0.75; $P = .007$). Again, no significant difference in rates of major bleeding was reported.

Glioma. The PRODIGE trial included 186 patients with newly diagnosed grade 3 or 4 glioma and was terminated early.[23] Patients were randomly assigned to dalteparin or placebo for 6 months, and therapy could continue for an additional 6 months. VTE events occurred in nine patients (9%) in the dalteparin arm compared with 13 patients (15%) in the placebo arm (HR, 0.51; 95% CI, 0.19 to 1.40; $P = .29$). Five patients in the dalteparin arm experienced intracranial bleeding by 12 months compared with one in the control arm (HR, 4.2; 95% CI, 0.48 to 36; $P = .22$).

Overall, the Panel concluded that offering all patients with solid malignancies anticoagulation for thromboprophylaxis in the ambulatory setting is not justified based on the available clinical trial data and the heterogeneity of this patient population.

Multiple myeloma. Two RCT substudies assessed different thromboprophylaxis strategies in patients with newly diagnosed multiple myeloma receiving lenalidomide- or thalidomide-based treatment.[20,22] Palumbo et al[22] stratified patients on the basis of age and transplantation eligibility and then randomly assigned them to one of two chemotherapy regimens. Patients who received thalidomide-based regimens were eligible for random assignment to warfarin, low-dose aspirin, or enoxaparin. Of 659 analyzed patients, serious thromboembolic events, acute cardiovascular events, or sudden death during the first 6 months occurred in 6.4% in the aspirin group, 8.2% in the warfarin group, and 5.0% in the LMWH group. Compared with LMWH, the absolute differences were 1.3% (95% CI, 3.0% to 5.7%; $P = .544$) with aspirin and 3.2% (95% CI, 1.5% to 7.8%; $P = .183$) with warfarin. Three major bleeding episodes occurred with aspirin (1.4%) compared with none in the other arms.[22] No difference in the risk of VTE was found when comparing aspirin with LMWH (HR, 1.13; 95% CI, 0.59 to 2.17).

In the other study from the same group, 342 patients with newly diagnosed multiple myeloma treated with lenalidomide-based chemotherapy were randomly assigned to either prophylactic low-dose aspirin (100 mg per day) or enoxaparin during induction and consolidation chemotherapy.[20] Symptomatic VTE was reported in 2.3% of patients receiving aspirin and 1.2% receiving LMWH for an absolute difference of 1.07% (95% CI, −1.69 to 3.83; $P = .452$). No major

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bleeding was reported in either arm, and minor bleeding was noted in one patient receiving enoxaparin.

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 considered for pharmacologic thromboprophylaxis with either UFH or LMWH unless contraindicated because of active bleeding or high bleeding risk.

Recommendation 3.2

Prophylaxis should be commenced preoperatively.

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.

Recommendation 3.4

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

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 should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors as listed in Table 3. In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis considering the individual patient.

Literature Update and Analysis 3

Six meta-analyses[27-32] and three RCTs[33-35] of perioperative prophylaxis in patients with cancer were identified by the updated systematic review. Three of the meta-analyses[28,30,31] and one of the RCTs considered extended perioperative thromboprophylaxis.[33]

Primary Prophylaxis

A Cochrane meta-analysis comparing prophylactic LMWH with UFH in the cancer perioperative setting found little difference in rates of PE and DVT.[32] Major bleeding was also similar with the two anticoagulants (RR, 0.84; 95% CI, 0.52 to 1.36). A systematic review limited to patients undergoing surgery for gynecologic cancer compared UFH, LMWH, or sequential compression devices with either untreated controls or one another.[29] A reduction in DVT with UFH compared with untreated controls was observed (RR, 0.58; 95% CI, 0.35 to 0.95), but there was no difference between UFH and LMWH (RR, 0.91; 95% CI, 0.38 to 2.17). Bleeding rates were not reported.

The three RCTs that assessed primary perioperative prophylaxis included patients undergoing abdominal or pelvic surgery. In the Sakon et al[34] trial, 164 patients with cancer undergoing abdominal laparotomy were randomly assigned to enoxaparin or intermittent pneumatic compression (IPC). The incidence of symptomatic VTE was 1.2% (95% CI, 0.03 to 6.53%) in the enoxaparin group and 19.4% (95% CI, 7.45 to 37.47%) in the IPC group. Major bleeding was reported in 4.6% (95% CI, 1.5% to 10.4%) in the enoxaparin group and 2.6% (95% CI, 0.1% to 13.8%) in the IPC group. The SAVE-ABDO (Evaluation of AVE5026 as Compared to Enoxaparin for the Prevention of Venous Thromboembolism in Patients Undergoing Major Abdominal Surgery)[33] and Simonneau et al[35] trials compared two different LMWH regimens. SAVE-ABDO was a randomized, double-blind, phase III trial of 4,414 patients undergoing major abdominal surgery, of whom 81% underwent surgery for malignant disease. Patients were randomly assigned to either ultra-LMWH semuloparin starting before surgery or enoxaparin starting after surgery. The primary outcome of any VTE and all-cause mortality occurred in 5.5% of those receiving enoxaparin and 6.3% receiving semuloparin (OR, 1.16; 95% CI, 0.84 to 1.59). There were fewer events of major bleeding with semuloparin (OR, 0.63; 95% CI, 0.46 to 0.87). In the double-blind Simonneau et al study, patients with colorectal cancer were randomly assigned to nadroparin or enoxaparin, both starting before surgery.[35] Of 1,288 patients randomly assigned, only 950 (73.8%) were analyzed, with symptomatic and asymptomatic VTE rates of 15.9% with nadroparin and 12.6% with enoxaparin for a relative risk of 1.27 (95% CI, 0.93 to 1.74; not significant). Major bleeding was reported in 11.5% of patients receiving enoxaparin and 7.3% receiving nadroparin (RR, 0.64; 95% CI, 0.45 to 0.91; $P = .012$).

These surgical studies were conducted in patients with GI, gynecologic, or urologic malignancies undergoing major cancer surgeries and examined thromboprophylaxis administered for approximately 7 to 10 days. This duration was established in historical trials of primary prophylaxis in the surgical setting.[36-44] There are no studies assessing shorter durations or limiting thromboprophylaxis during the hospitalization for lower risk cancer surgery.

Extended Prophylaxis

Three systematic reviews of extended prophylaxis, for 4 weeks postoperatively with LMWH in mixed cancer and noncancer populations, were reported.[28,30,31] The meta-analysis by Bottaro et al[28] included three trials involving 1,104 patients, 70.6% of whom had cancer. A decrease in asymptomatic and symptomatic VTE among patients with cancer was noted in a subgroup analysis (RR, 0.46; 95% CI, 0.28 to 0.77). Major bleeding was not significantly different in the treatment groups overall (RR, 0.83; 95% CI, 0.22 to 3.12), although no cancer-specific rates were reported. Akl et al[31] included three trials or subgroups of trials representing patients with cancer and reported a decrease in the risk of asymptomatic DVT with extended LMWH prophylaxis versus untreated control or placebo (RR, 0.21; 95% CI, 0.05 to 0.94). No significant difference in the risk of major bleeding was reported (RR, 2.94; 95% CI, 0.12 to 71.85). Rasmussen et al[30] included one additional trial in their meta-analysis but did not present results specifically among patients with cancer undergoing surgery. The incidence of asymptomatic and symptomatic VTE after major abdominal or pelvic surgery was 14.3% among controls and 6.1% among those receiving extended prophylaxis with LMWH (OR, 0.41; 95% CI, 0.26 to 0.63; $P < .001$). Although major bleeding events were not presented separately, all bleeding events in the control and LMWH

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groups were 3.7% (95% CI, 2.4% to 5.5%) and 4.1% (95% CI, 2.7% to 6.0%), respectively (OR, 1.11; 95% CI, 0.62 to 1.97; $P = .73$).

The more recent CANBESURE (Cancer, Bemiparin, and Surgery Evaluation) study randomly assigned 626 patients undergoing abdominal or pelvic cancer surgery to either extended thromboprophylaxis with bemiparin (28 days) or bemiparin (8 days) in a double-blind fashion.[45] The primary outcome of asymptomatic or symptomatic DVT, nonfatal PE, or all-cause mortality during the double-blind period occurred in 10.1% of patients receiving bemiparin and 13.3% of those in the placebo group, and the primary end point was not met (RR, 0.75; 95% CI; 0.46 to 1.24; $P = .26$). Major bleeding was reported in two patients (0.6%) receiving bemiparin and one (0.3%) in the placebo arm (not significant). While the study was underway, but before unblinding, a secondary outcome of major VTE was defined as asymptomatic proximal or symptomatic proximal DVT, nonfatal PE, and VTE-related death. At the end of the double-blind period, major VTE was reported in two (0.8%) and 11 (4.6%) patients, respectively (RR, 0.18; 95% CI; 0.04 to 0.78; $P = .010$).

CLINICAL QUESTION 4

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

Recommendation 4.1

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).

Recommendation 4.2

For long-term anticoagulation, LMWH for at least 6 months is preferred because of improved efficacy over VKAs. VKAs are an acceptable alternative for long-term therapy if LMWH is not available.

Recommendation 4.3

Anticoagulation with LMWH or VKAs beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.

Recommendation 4.4

The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy (Table 4). It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal therapy with LMWH.

Recommendation 4.5

For patients with primary CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications.

Recommendation 4.6

Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time.

Table 4. Contraindications and Other Considerations to Withhold Therapeutic Anticoagulant Therapy in Patients With Cancer and VTE*

Contraindication/Consideration
Absolute contraindications†
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 (ie, 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)
Surgery or invasive procedure, including but not limited to lumbar puncture, spinal anesthesia, and epidural catheter placement
Relative contraindications‡
Intracranial or spinal lesion at high risk for bleeding
Active peptic or other GI ulceration at high risk of bleeding
Active but non–life-threatening bleeding (eg, trace hematuria)
Intracranial or CNS bleeding within past 4 weeks
Major surgery or serious bleeding within past 2 weeks
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

Abbreviation: VTE, venous thromboembolism.
*These criteria are specific for therapeutic doses of anticoagulation and should not be applied to prophylactic doses of anticoagulation.
†Absolute contraindications are situations in which anticoagulation should not be administered because the risk of harm associated with bleeding is likely to exceed the potential benefit from anticoagulation.
‡Relative contraindications are situations in which anticoagulation may be administered if the risk of recurrent or progressive thrombosis is estimated to exceed the risk of bleeding.

Recommendation 4.7

Based on consensus, incidental PE and DVT should be treated in the same manner as symptomatic VTE. Treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.

Literature Update and Analysis 4

Three systematic reviews relevant to VTE treatment and secondary prophylaxis were identified.[46-48] No new RCTs that met inclusion criteria were identified.

Systematic Reviews

Data on the relative efficacy and safety of LMWH and UFH for initial treatment in patients with cancer come from post hoc subgroup analysis of large RCTs.[48] Differences in recurrent thrombosis and bleeding were not observed. However, a reduction in mortality with LMWH compared with UFH at 3 months of follow-up was estimated (RR, 0.71; 95% CI, 0.52 to 0.98). A systematic review and meta-analysis comparing LMWH and VKAs for long-term anticoagulation was reported by the Cochrane Collaboration.[47] The rate of recurrent

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thromboembolism was lower with LMWH (RR, 0.49; 95% CI, 0.34 to 0.70), but the rates of mortality and bleeding were similar.

Romera-Villegas et al[46] assessed LMWH dose (full, intermediate, or prophylactic) compared with VKAs for long-term VTE treatment. LMWH at full (RR, 0.37; 95% CI, 0.19 to 0.74) or intermediate (RR, 0.52; 95% CI, 0.35 to 0.79) dose was superior to a VKA. No difference between prophylactic doses of LMWH and VKA was found based on small numbers of patients. Indirect comparison revealed no differences in major bleeding between the LMWH doses.

Initial and Long-Term Treatment Up to 6 Months

For initial therapy in patients with established VTE without renal impairment (creatinine clearance > 30 mL/min), a Cochrane meta-analysis found improved survival with LMWH over UFH in patients with cancer.[48] However, a small RCT in elderly patients with renal insufficiency (only 6% with cancer) reported higher mortality with tinzaparin compared with UFH (see Special Populations).[49] For treatment up to 6 months, meta-analyses and RCTs validate superiority of LMWH over VKAs.[47,50-52]

Data on other anticoagulants for patients with cancer are limited. Fondaparinux has been used for initial[53] and extended therapy for VTE[54] in patients with cancer. The numbers of patients in these reports were small. Nonetheless, although fondaparinux may be an alternative for patients with heparin-induced thrombocytopenia, it does not have a US Food and Drug Administration indication in this setting.

Treatment Beyond 6 Months

No published studies address optimal anticoagulation beyond the first 6 months in patients with cancer. However, it is the consensus of the Panel, based on extrapolation from patients with idiopathic 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 of bleeding, cost of therapy, quality of life, life expectancy, and patient preference.

Novel Oral Anticoagulants

Novel anticoagulants that target thrombin (direct thrombin inhibitor dabigatran) or activated factor X (antifactor Xa inhibitors rivaroxaban, apixaban, and edoxaban) are now approved for selected indications in VTE prevention and treatment. However, RCTs evaluating these drugs for VTE treatment included few patients with malignant disease: RECOVER (Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism) study of dabigatran, 5%[55]; EINSTEIN trials of rivaroxaban, 6.8% (DVT; Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis), 4.7% (PE; Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism), and 4.7% (Extended Treatment; Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism)[56,57]; and AMPLIFY-EXT (Apixaban After Initial Management of PE and VTE With First-Line Therapy–Extended Treatment) trial of apixaban, 1.8% (2.5 mg) and 1.1% (5 mg).[58] Additional concerns with using these agents in patients with cancer include: unpredictable absorption and higher risk of GI bleeding in those with mucositis or other GI complications, altered metabolism in those with liver or renal impairment, drug interaction with hormonal and chemotherapeutic agents, inability to measure the anticoagulant activity using standard assays, and lack of an antidote. In a placebo-controlled pilot study of primary prophylaxis with apixabain for 3 months in patients with advanced or metastatic cancer, Levine et al[59] reported major bleeding in only 2.2% of patients. Nonetheless, adequately powered RCTs are needed to examine the efficacy and safety of these drugs in patients with cancer.

Recurrent VTE

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. Otherwise, management options include treatment with an alternate anticoagulant regimen, increasing the dose of LMWH, or adding a vena cava filter to LMWH. In patients for whom standard doses of LMWH fail, higher doses should be considered and are generally well tolerated in those without an increased risk of bleeding. In a retrospective study of patients with cancer and recurrent thrombosis, increasing the LMWH dose by 20% to 25% was effective in preventing further recurrence.[60]

Incidental VTE

Incidental findings of PE and/or DVT during routine staging with computed tomography scans of abdomen and pelvis as well as splanchnic or visceral vein thrombi are frequently reported. In a recent large systematic review and meta-analysis of 12 studies including > 10,000 patients, those had a weighted mean prevalence of incidental PE of 3.1% (95% CI, 2.2 to 4.1%).[61] In a retrospective cohort analysis by Moore et al,[62] 44% of all thromboembolic events were incidental. In a cohort study by Singh,[63] 50% of DVTs and > 35% of PEs were incidentally discovered. The pulmonary distribution of incidental emboli is no different from that of symptomatic emboli, with nearly half occurring in major pulmonary vessels.[64,65] Importantly, rates of VTE recurrence, bleeding, and mortality seem to be similar in patients with cancer and incidental VTE compared with those with symptomatic VTE.[64-68]

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.[69] 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.[54] Cohort studies in patients with cancer suggest much higher rates of recurrent VTE and no survival advantage with filters.[70] It remains unclear 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 retrievable filters has raised serious concerns. In 2010, the US Food and Drug Administration released a safety alert for optional recovery filters in response to the high number of adverse events reported.[71]

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Intracranial Malignancy

Patients with intracranial tumors are at increased risk for thrombotic complications and intracranial hemorrhage. However, presence of an intracranial tumor or brain metastasis is not an absolute contraindication to anticoagulation. Limited data support use of antithrombotic therapy in patients with primary or metastatic brain tumors who develop concurrent venous thrombosis.[72-77] A high failure rate has been reported with IVC filters, without improved overall survival or reduced intracranial hemorrhage in small retrospective series.[74,75,77]

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, cognitive decline, and without family or nearby support.

The elderly. The IRIS (Innohep in Renal Insufficiency Study) trial comparing tinzaparin with UFH for initial therapy in patients age $\geq$ 70 years with renal impairment was terminated early because of an excess number of deaths in the tinzaparin group.[49] Poor prognosis factors, including cancer, were over-represented in the tinzaparin arm. Because of early termination, the study was underpowered to detect differences in clinically relevant bleeding and recurrent VTE.

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 $<$ 30 mL/min and that the risk of bleeding in these patients is at least two-fold higher than in patients with normal creatinine clearance.[78] Studies indicate that enoxaparin requires dose reduction, but tinzaparin does not.[79-81] Data on dalteparin at therapeutic doses in patients with renal impairment are lacking. Anti-Xa monitoring 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.

Obesity. In obese patients, LMWH dosing has not been well studied. Cohort studies using enoxaparin and dalteparin suggest that LMWH dose should be based on a patient's actual body weight.[82,83] Bleeding risk does not seem to be higher in obese patients.

CLINICAL QUESTION 5

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

Recommendation 5.1

Anticoagulants are not recommended to improve survival in patients with cancer without VTE.

Recommendation 5.2

Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.

Literature Update and Analysis 5

The updated systematic review identified three systematic reviews[84-86] and one RCT.[87] All included patients who did not have any indication for anticoagulation.

The systematic review and meta-analysis from Kuderer et al[84] evaluated the impact of anticoagulation on survival. The general comparison of any anticoagulation with no therapy—as well as the more specific LMWH or warfarin versus no therapy—demonstrated a lower mortality risk at 1 year with anticoagulation. Bleeding rates were higher with any anticoagulation (RR, 2.31; 95% CI, 1.93 to 2.76).

Two Cochrane reviews were published on this topic; one evaluated survival with oral anticoagulation and the other with parenteral agents.[85,86] Comparisons of warfarin with no therapy showed no significant differences in mortality or the incidence of VTE. As expected, warfarin was associated with increased bleeding. In the comparisons of UFH or LMWH versus placebo, a decrease in mortality was noted at 2 years (RR, 0.92; 95% CI, 0.88 to 0.97). This decrease was also noted in the small subgroup of patients with small-cell lung cancer (RR, 0.86; 95% CI, 0.75 to 0.98).

One RCT included patients with advanced lung, hormone-refractory prostate, or pancreatic cancer and life expectancy $<$ 6 months.[87] Patients were randomly assigned to 6 weeks of LMWH or no treatment. No benefit in overall survival was noted (HR, 0.94; 95% CI, 0.75 to 1.18). This trend was consistent in the subgroup analysis by cancer type.

CLINICAL QUESTION 6

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

Recommendation 6.1

Based on consensus, the Panel recommends that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. Individual risk factors, including biomarkers and cancer site, do not reliably identify patients with cancer at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool (Table 5).

Recommendation 6.2

Based on consensus, the Panel recommends that oncologists educate patients regarding VTE, particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy.

Literature Update and Analysis 6

The risk systematic review identified five cohort studies.[62,88-91] Two reported development of new risk assessment models,[88,89] and three evaluated existing models.[62,90,91] The International Myeloma Working Group proposed a consensus-based risk assessment algorithm to categorize risk among patients with myeloma; validation is awaited.[92] Several VTE risk assessment tools have been developed and validated in the perioperative setting, but none has specifically focused on patients with cancer.[93]

Multiple cancer-, treatment-, and patient-related risk factors for VTE relevant to various cancer populations are summarized in Table 3.[91,94-96] Although patients with brain, pancreatic, stomach, kidney,

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Table 5. Predictive Model for Chemotherapy-Associated VTE in the Ambulatory Setting

Patient Characteristic	Points
Site of cancer	
Very high risk (stomach, pancreas, primary brain tumor)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal tumors)	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 ≥ 3 points	
Intermediate risk, 1 to 2 points	
Low risk, 0 points	

NOTE. Data adapted.[88]
Abbreviation: VTE, venous thromboembolism.

ovarian, or lung cancer are commonly considered at high risk for VTE, patients with hematologic malignancies are also at elevated risk.[97,98] Hospitalization or major surgery can lead to a transient increase in risk.[2,3,27-32,34,35,45,99] Specific therapeutic agents such as thalidomide,[22] lenalidomide,[20] and cisplatin[62,100] can also increase VTE risk. Although a number of biomarkers have been evaluated, neither solitary risk factors nor individual biomarkers reliably identify high-risk patients.[101-103]

A multivariable clinical risk assessment model for VTE was developed and internally validated in a cohort of ambulatory patients with cancer receiving systemic chemotherapy (Table 5).[88] This model has now been externally validated for predicting risk of VTE by several investigators.[90,91] The balance of benefit and harm with thromboprophylaxis for high-risk patients identified by the model is under study. Therefore, routine thromboprophylaxis in this setting is not currently recommended.

PATIENT AND CLINICIAN COMMUNICATION

Despite the well-known association of VTE and cancer, patients are woefully unaware of that risk and of warning signs and symptoms. Two patient surveys found that fewer than half of patients were aware of the increased risk of VTE associated with malignancy.[105,106] In a survey of hospitalized patients receiving thromboprophylaxis, responders reported hearing about VTE more frequently from friends, family, or the media than from health care providers.[107] A different survey indicates that inpatients knew more about VTE than outpatients: 36% versus 15%.[106]

The need for increased patient education and awareness is clear. Educated patients are more likely to report symptoms that could lead to early intervention.[107] In addition, aware and educated patients are more likely to accept efforts such as anticoagulation or early mobility after surgery. In fact, a qualitative survey of patients with cancer noted that increased awareness of VTE led to increased acceptance of prophylactic LMWH. Many patients reported improved quality of life secondary to a feeling of safety and reassurance.[108]

Communicating with patients about the signs, symptoms, and risk of VTE is crucial. Oncologists, along with other health care professionals on the oncology team, should assure, at minimum, that patients have a basic recognition of VTE warning signs. Nurses are in an ideal position to educate patients.[109] Resources, including information sheets and symptom checklists, are available to facilitate such conversations. Respondents to the qualitative survey who were given educational materials or directed to such (15% of the sample) found those materials "very useful."[106]

Further education can help patients distinguish between symptoms secondary to their underlying disease, treatment, and other potential causes. Patients may not report new symptoms, unless queried directly, because they mistakenly assume 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 ensure effective communication as well as facilitate patient understanding.

HEALTH DISPARITIES

Rates of VTE are higher among African Americans than in the general population overall.[110,111] Rates are lower in the Asian population than in other ethnicities.[111] A nationwide analysis of nearly 500,000 patients with cancer in Taiwan recently described risk factors and a scoring system for this population.[112] Applicability of these findings to North American and European patients is unknown.

Although ASCO clinical practice guidelines represent expert recommendations on best practices 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. Minority racial/ethnic patients with cancer 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.[113-116] Many other patients lack access to care because of geography or distance from appropriate treatment facilities. Awareness of these disparities in 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.

LIMITATIONS

These recommendations are based on data identified by a systematic review of the literature. Some key questions are, as yet, unanswered. The potential benefits and harms of thromboprophylaxis in patients with cancer receiving chemotherapy in the outpatient setting and the utility of risk assessment require additional research. Future thromboprophylaxis trials in outpatients receiving chemotherapy may benefit from the identification of high-risk groups in whom the balance of benefits and harms favors prophylaxis.

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ADDITIONAL RESOURCES

The Data Supplement, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/vte. Patient information is also available there and at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors. Authors marked with an asterisk (*) are participants in ASCO's Disclosure Management System Pilot; their disclosure is not limited to subject matter under consideration in this article and includes payments to themselves, an immediate family member (I), and/or their institutions (INST). For information on the pilot program, or to provide feedback, please visit coipilot.asco.org.

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Appendix

Table A1. Panel Composition

Name	Expertise
Anna Falanga, MD, co-chair*	Hematology
Gary H. Lyman, MD, MPH, co-chair*	Hematology and medical oncology
Alok A. Khorana, MD*	Hematology and medical oncology
Nicole M. Kuderer, MD*	Hematology and medical oncology
Juan Ignacio Arcelus	Surgery
Edward P. Balaban, DO	Hematology and medical oncology
Jeffrey M. Clarke, MD	Medical oncology
Christopher R. Flowers, MD, MS	Hematology and medical oncology
Charles W. Francis, MD	Hematology and medical oncology
Leigh E. Gates, BA, CPHQ	Patient representative
Ajay K. Kakkar, MD, BS, PhD	Surgery
Nigel S. Key, MB, ChB, FRCP	Hematology and medical oncology
Agnes Y. Lee, MD, MSc, FRCPC	Hematology
Mark N. Levine, MD, MSc	Hematology and medical oncology
Howard A. Liebman, MD	Hematology and medical oncology
Margaret A. Tempero, MD	Hematology and medical oncology
Sandra L. Wong, MD	Surgical oncology

*Steering Committee member.

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