



AMERICAN SOCIETY OF CLINICAL ONCOLOGY



***Recommendations for Venous
Thromboembolism Prophylaxis and
Treatment in Patients with Cancer***

American Society of Clinical Oncology
Clinical Practice Guideline

Introduction

- ASCO convened an expert panel to develop guideline recommendations for the use of anticoagulation in the prevention and treatment of venous thromboembolism (VTE) in patients with cancer.

Guideline Methodology: Systematic Review

- A comprehensive systematic review of the medical literature available through December 2006 on anticoagulation and the prevention of VTE in patients with cancer was conducted.
 - ✓ Medline
 - ✓ EMBASE
 - ✓ CancerLit
 - ✓ Cochrane
 - ✓ Database of Abstracts of Reviews of Effects (DARE)
 - ✓ National Guidelines Clearing House

Guideline Methodology (cont'd): Panel Members

■ Gary H. Lyman, MD, MPH, FRCP (Edin), <i>Co-Chair</i>	■ Duke University
■ Anna Falanga, MD, <i>Co-Chair</i>	■ Ospedali Riuniti, Bergamo, Italy
■ Daniel Clarke-Pearson, MD	■ University of North Carolina
■ Christopher Flowers, MD, MS	■ Emory University
■ Charles W. Francis, MD	■ University of Rochester
■ Leigh Gates, <i>Patient Representative</i>	■ University of Colorado
■ Mohammad Jahanzeb, MD	■ University of Tennessee
■ Ajay Kakkar, MD, PhD	■ Barts and The London School of Medicine

Guideline Methodology (cont'd): Panel Members

■ Alok A. Khorana, MD	■ University of Rochester
■ Nicole M. Kuderer, MD	■ Duke University
■ Mark Levine, MD, PhD	■ McMaster University
■ Howard A. Liebman, MD	■ University of Southern California
■ David S. Mendelson, M.D.	■ Premiere Oncology
■ Gary Edward Raskob, PhD	■ University of Oklahoma
■ Paul A. Thodiyil, MD	■ New York Methodist Hospital
■ David Trent, MD, PhD	■ Virginia Cancer Center

Background

- Venous Thromboembolism (VTE)
 - A leading cause of morbidity and mortality in patients with cancer
 - Affects 4-20% of patients with cancer
 - Appears to be increasing
- Burden
 - Mortality
 - Morbidity
 - Other health outcomes
 - Use of health care resources

Background

■ Major Risk Factors

- Age
- Primary site of cancer (gastrointestinal, brain, lung, gynecologic, pancreatic, gastrointestinal, ovarian, renal, bladder, hematologic)
- History of VTE
- Hospitalization
- Major surgery
- Those receiving active therapy, including chemotherapy, antiangiogenic drugs, and hormonal therapy
- Metastatic disease
- Red cell growth factors

■ Challenges and Opportunities

- Primary prophylaxis can reduce DVT, PE, and fatal PE
- Prophylaxis under-utilized

Clinical Questions

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

2007 Recommendations for Venous Thromboembolism Prophylaxis in Patients with Cancer

- Hospitalized patients with cancer should be considered candidates for VTE prophylaxis in the absence of bleeding or other contraindications to anticoagulation.

2007 Recommendations for Venous Thromboembolism Prophylaxis in Patients with Cancer

■ Ambulatory patients with cancer:

1. Routine prophylaxis with an antithrombotic agent is not recommended.
2. Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at high risk for thrombosis and warrant prophylaxis. LMWH (low molecular weight heparin) or adjusted dose warfarin (INR~1.5) is recommended.
 - *This recommendation is based on extrapolation from studies of post-operative prophylaxis in orthopedic surgery and a trial of adjusted dose warfarin in patients with breast cancer.*
3. Randomized clinical trials evaluating antithrombotic agents in patients with multiple myeloma on thalidomide or lenalidomide are needed.
4. Research is also urgently needed to identify better markers in ambulatory patients with cancer who are most likely to develop VTE.

2007 Recommendations for Venous Thromboembolism Prophylaxis in Patients with Cancer, Continued

■ Patients undergoing surgery:

1. All patients undergoing major surgical intervention* for malignant disease should be considered for thromboprophylaxis.
2. Eligible patients should receive pharmacological thromboprophylaxis with either low dose UFH (unfractionated heparin) or LMWH unless contraindicated because of a high risk for or active bleeding.
3. Prophylaxis should be commenced preoperatively, or as early as possible in the postoperative period.

*laparotomy, laparoscopy or thoracotomy lasting greater than 30 minutes

2007 Recommendations for Venous Thromboembolism Prophylaxis in Patients with Cancer, Continued

■ Patients undergoing surgery, continued:

4. Mechanical methods may be added to pharmacological methods, but should not be used as monotherapy for VTE prevention unless pharmacological methods are contraindicated because of active bleeding.
5. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy in the patients at highest-risk.
6. Prophylaxis should be continued for at least 7-10 days postoperatively and may be extended into the post discharge period for selected patients at high risk.**

**residual malignant disease after operation, obesity, or previous history of VTE

2007 Recommendations for Venous Thromboembolism Prophylaxis in Patients with Cancer, Continued

- Preventing recurrence in patients with cancer with established VTE
 1. LMWH is the preferred approach for the initial 5 to 10 days of anticoagulant treatment of the patient with cancer with established VTE.
 2. LMWH given for at least 6 months is also the preferred approach for long-term anticoagulant therapy. Vitamin K antagonists with a targeted INR of 2-3 are acceptable for long-term therapy when LMWH is not available.
 3. After 6 months, indefinite anticoagulant therapy should be considered for patients with active cancer.
 4. 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.

2007 Recommendations for Venous Thromboembolism Prophylaxis in Patients with Cancer, Continued

- Preventing recurrence in patients with cancer with established VTE, continued
5. In patients with central nervous system malignancies and in the elderly, anticoagulation is recommended for established VTE as described for other patients with cancer .
 6. Careful monitoring of anticoagulation is necessary to limit the risk of hemorrhagic complications.
 7. Anticoagulation should be avoided in the presence of active intracranial bleeding or preexisting bleeding diathesis such as thrombocytopenia (platelet count $<50,000/\text{mm}^3$) or coagulopathy.

2007 Recommendations for Venous Thromboembolism Prophylaxis in Patients with Cancer, Continued

■ Improving survival in absence of established VTE

1. Anticoagulants are not recommended to improve survival in patients with cancer without VTE.
2. People with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.

Recommended Dose: Venous Thromboembolism Prophylaxis/Treatment

Management	Drug	Regimen
Prophylaxis		
Patients with cancer receiving medical or surgical treatment while staying in hospital	Unfractionated Heparin (UFH)	5000 U q 8 h
	Dalteparin (Fragmin®)	5000 U daily
	Enoxaparin (Lovenox®)	40 mg daily
	Fondaparinux (Arixtra®)	2.5 mg daily
Treatment		
Initial	Dalteparin (Fragmin®)	100 U/kg q 12 hr
		200 U/kg daily
	Enoxaparin (Lovenox®)	1 mg/kg q 12 hr
		1.5 mg/kg daily

Recommended Dose: Venous Thromboembolism Prophylaxis/Treatment

Management	Drug	
Initial treatment, cont'd.	Heparin	80 U/kg IV bolus, then 18 U/kg/hr IV [adjust level based on PTT]
	Fondaparinux (Arixtra®)	<50 kg, 5 mg daily
		50-100 kg, 7.5 mg daily
		>100 kg, 10 mg daily
Long-Term Treatment	Tinzaparin (Innohep®)	175 U/kg daily
	Dalteparin (Fragmin®)	200 U/kg daily for 1 m; then 150 U/kg daily for 5 m
	Warfarin	5-10 mg po daily; adjust dose to INR 2-3

Relative contraindications for anticoagulation

- Active, uncontrollable bleeding
- Active cerebrovascular hemorrhage
- Dissecting or cerebral aneurysm
- Bacterial endocarditis
- Pericarditis, active peptic or other GI ulceration
- Severe, uncontrolled or malignant hypertension
- Severe head trauma
- Pregnancy (warfarin)
- Heparin-induced thrombocytopenia (heparin, LMWH)
- Epidural catheter placement

Types of Mechanical Methods

- Graduated compression stockings
- Intermittent pneumatic compression (IPC)
- Mechanical foot pumps

Special Considerations

Situation	Consideration
Women with gynecologic malignancy	Mechanical and pharmacologic methods in combination
Patients with CNS malignancies and the elderly patient cancer	Careful monitoring and caution Mechanical and pharmacologic methods in combination
Patients with multiple myeloma receiving thalidomide or lenalidomide with chemotherapy or dexamethasone who are ambulatory	Prophylaxis recommended
Patients undergoing major abdominal or pelvic surgery for cancer at high risk, such as residual malignant disease, patients with obesity, and patients with history of VTE	Prolonged prophylaxis – up to four weeks

Summary

Patient Group	Recommended	Not Recommended
Hospitalized patients with cancer	VTE prophylaxis with anticoagulants	If patient bleeding or has contraindication to anticoagulation
Ambulatory patients with cancer receiving chemotherapy	For those with multiple myeloma receiving thalidomide or lenalidomide plus chemotherapy or dexamethasone. LMWH or adjusted dose warfarin.	Otherwise, no routine prophylaxis
Patients with cancer undergoing surgery	<p>Prophylaxis with low-dose UFH or LMWH</p> <p>Prophylaxis with mechanical methods for patients with contraindications to pharmacologic methods</p>	If patient bleeding or has contraindication to anticoagulation. Consider mechanical methods alone for those with contraindications to pharmacologic methods.
Patients with cancer with established VTE	Pharmacologic treatment for at least 6 months (LMWH or Vitamin K with targeted INR of 2-3 if LMWH not available). Consider continued anticoagulation beyond 6 months in those with with active cancer.	-
Patients with cancer without VTE to improve survival	-	Not recommended

Additional ASCO Resources

- This slide set and additional resources can be accessed at:
<http://www.asco.org/guidelines/vte>
- Access the *People Living With Cancer* website for a Patient Guide and other patient-friendly information at
<http://www.plwc.org>



ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.