ASCO SPECIAL ARTICLE

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

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ABSTRACT

Purpose
To develop guideline recommendations for the use of anticoagulation in the prevention and treatment of venous thromboembolism (VTE) in patients with cancer.

Methods
A comprehensive systematic review of the medical literature on the prevention and treatment of VTE in cancer patients was conducted and reviewed by a panel of content and methodology experts. Following discussion of the results, the panel drafted recommendations for the use of anticoagulation in patients with malignant disease.

Results
The results of randomized controlled trials of primary and secondary VTE medical prophylaxis, surgical prophylaxis, VTE treatment, and the impact of anticoagulation on survival of patients with cancer were reviewed. Recommendations were developed on the prevention of VTE in hospitalized, ambulatory, and surgical cancer patients as well as patients with established VTE, and for use of anticoagulants in cancer patients without VTE to improve survival.

Conclusion
Recommendations of the American Society of Clinical Oncology VTE Guideline Panel include (1) all hospitalized cancer patients should be considered for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications; (2) routine prophylaxis of ambulatory cancer patients with anticoagulation is not recommended, with the exception of patients receiving thalidomide or lenalidomide; (3) patients undergoing major surgery for malignant disease should be considered for pharmacologic thromboprophylaxis; (4) low molecular weight heparin represents the preferred agent for both the initial and continuing treatment of cancer patients with established VTE; and (5) the impact of anticoagulants on cancer patient survival requires additional study and cannot be recommended at present.

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INTRODUCTION

Venous thromboembolism (VTE) is a major complication of cancer, occurring in 4% to 20% of patients, and is one of the leading causes of death in patients with cancer.[1] The risk of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE) is increased several-fold in patients with cancer.[2] Hospitalized patients with cancer and those receiving active therapy seem to be at the greatest risk for development of VTE. In a population-based study, cancer was associated with a 4.1-fold greater risk of thrombosis, whereas the use of chemotherapy increased the risk 6.5-fold.[2,3] Of all patients with VTE, patients with cancer account for

20%, with patients receiving chemotherapy accounting for as much as 13% of the total burden of VTE.[4,5] The reported rates of VTE in patients with cancer are believed to be underestimated, given that autopsy rates of VTE can be as high as 50% compared with clinical rates of 4% to 20%.[6-8] Furthermore, the burden of VTE in cancer seems to be increasing for uncertain reasons. In a recent analysis of more than 66,000 patients with cancer hospitalized at 120 US academic medical centers, 5.4% developed VTE per hospitalization, increasing by 36% from 1995 to 2002 ($P < .0001$ for trend).[1] Similarly, an analysis of the National Hospital Discharge Survey found that the incidence of VTE increased nearly two-fold from 1980 to 1999.[9] Vascular toxicity,

particularly thromboembolism, is a specific toxicity of antiangiogenic drugs. Newer cancer regimens that include thalidomide, lenalidomide, or bevacizumab have reported very high rates of VTE.[10-13]

CONSEQUENCES OF CANCER-ASSOCIATED VTE

The diagnosis of VTE has important clinical implications. In a prospective observational study of ambulatory patients with cancer initiating chemotherapy, venous and arterial thromboembolism together accounted for 9% of deaths.[1] Cancer diagnosed at the same time as, or within 1 year of an episode of VTE, is associated with a three-fold greater mortality at 1 year.[14] Hospitalized patients with VTE have a greater in-hospital mortality rate (odds ratio, 2.01; 95% CI 1.83 to 2.22; $P < .0001$), and this is true of patients both with and without metastatic disease.[15] The risk of fatal PE in patients with cancer undergoing surgery is three-fold greater than in patients without cancer undergoing similar surgery.[16] In addition, VTE recurs three-fold more frequently in cancer patients than in patients who do not have cancer, and requires long-term anticoagulation with a two-fold greater risk of bleeding complications than in patients who do not have cancer.[17] VTE in patients with cancer also consumes health care resources. In a retrospective analysis, the mean length of DVT-attributable hospitalization was 11 days, and the average cost of hospitalization for the index DVT episode was $20,065 in 2002 US dollars.[18] Reducing VTE in patients with cancer could therefore have a significant impact on morbidity, outcomes, use of health care resources and, above all, mortality. This guideline reviews the evidence base regarding risk factors, prevention, and treatment of VTE in patients with cancer, and provides clinical recommendations based on this evidence. Central venous catheter–associated thrombosis is an important complication of treatment in patients with cancer but is reviewed in a separate American Society of Clinical Oncology (ASCO) guideline on central venous catheters and will not be addressed here.

RISK FACTORS FOR CANCER-ASSOCIATED VTE

The risk of thrombosis differs across various cancer subgroups and over the natural history of the disease. The risk of VTE is highest in the initial period after the diagnosis of malignancy.[19,20] The association of VTE with specific sites of cancer such as pancreas, stomach, brain, ovary, kidney, and lung, and with the presence of metastatic disease, has been well documented.[9,15,21-23] Newer studies suggest a strong association with hematologic malignancies, particularly lymphomas.[15,19]

Patients with cancer receiving active therapy are at a greater risk for VTE. In a population-based study, chemotherapy was associated with a 6.5-fold increased risk of VTE.[2,3] Studies of newer cancer regimens, particularly those including antiangiogenic agents, have reported very high rates of VTE.[10-13] Hormonal therapy, particularly tamoxifen, has been associated with an increased risk of VTE. Erythropoiesis-stimulating agents are also associated with an increased risk of VTE; an association of myeloid growth factors with VTE has not been fully established.[21,24,25] The risk of VTE increases significantly when patients with cancer are hospitalized.[26] Patients with cancer undergoing surgery have a two-fold increased risk of postoperative DVT and a three-fold greater risk of fatal PE compared with patients who do not have cancer having similar surgery.[16] Other possible risk factors include a prechemotherapy platelet count $\geq 350,000/\mu L$[21] and the presence of prothrombotic mutations.[19,27] A comprehensive list of risk factors associated with VTE in patients with cancer is summarized in Table 1. Although a detailed discussion of the diagnostic process in patients with cancer at risk for VTE is beyond the scope of this guideline, symptomatic patients should be evaluated promptly. Symptoms suggestive of DVT include unilateral calf, leg, or thigh swelling or pain, whereas a diagnosis of DVT is generally based on a lower-extremity Doppler ultrasound. Symptoms suggestive of a PE include shortness of breath, tachypnea, pleuritic chest pain, a

Table 1. Risk Factors for VTE in Patients With Malignant Disease

Patient-related factors
Older age[15]
Race (higher in African Americans; lower in Asian-Pacific Islanders)[20]
Comorbid conditions (obesity, infection, renal disease, pulmonary disease, arterial thromboembolism)[15,21,26,33]
Prior history of VTE[26]
Elevated prechemotherapy platelet count[21]
Heritable prothrombotic mutations[19,34-36]
Cancer-related factors
Primary site of cancer (GI, brain, lung, gynecologic, renal, hematologic)[9,15,19-21,23]
Initial 3-6 months after diagnosis[19,20,33]
Current metastatic disease[15,19,20,23,33,37]
Treatment-related factors
Recent major surgery[32,38,39]
Current hospitalization[15,26,40]
Active chemotherapy[2,23,26,37]
Active hormonal therapy[37,41-43]
Current or recent antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab*)[11,28-31,44-46]
Current erythropoiesis-stimulating agents[21,24]
Presence of central venous catheters[32,47-49]

Abbreviation: VTE, venous thromboembolism.
*Bevacizumab is clearly associated with an increased risk of arterial thrombotic events; an association with venous thrombosis is not fully established.

pleural rub, hypoxia, hemoptysis, tachycardia, syncope along with accompanying symptoms, and signs of a DVT or right heart failure. A diagnosis of PE is generally based on a ventilation/perfusion scan or spiral computed tomography scan.

VARIATION IN CLINICAL PRACTICE

Multiple randomized trials in a variety of patient populations have been conducted in the last 30 years demonstrating that primary prophylaxis can reduce DVT, PE, and fatal PE.[50-54] The American College of Chest Physicians (ACCP) guidelines on prevention of VTE recommend prophylaxis for acutely ill hospitalized medical or surgical patients with cancer.[55] Surveys of oncologists, however, show low rates of compliance with thromboprophylaxis.[56,57] This may be related to under-recognition of prevalent risk factors, concern regarding the risk of bleeding, and lack of awareness of these guidelines within the oncology community. Identification of patients most at risk for VTE followed by institution of effective prophylaxis could have a significant impact on morbidity, delivery of cancer therapy, cancer-related outcomes, use of health care resources and, above all, mortality in patients with cancer.[58]

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?

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide:

(1) Improvements in outcomes
(2) Improvements in medical practice
(3) A means for minimizing inappropriate practice variation
(4) Decision support tools for practitioners
(5) Points of reference for medical orientation and education
(6) Criteria for self-evaluation
(7) Indicators and criteria for external quality review
(8) Assistance with reimbursement and coverage decisions
(9) Criteria for use in credentialing decisions

In formulating recommendations for the appropriate use of VTE prophylaxis and treatment in patients with cancer, ASCO considered these tenets, emphasizing a review of data from appropriately con-

ducted and analyzed clinical trials. However, it is important to emphasize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment regarding 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 result. Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's circumstances. In addition, these guidelines describe the use of procedures and therapies in clinical practice; they cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved management is needed. Because guideline development involves a review and synthesis of the literature, a practice guideline also serves to identify important questions and settings for further research.

METHODS

PANEL COMPOSITION

The ASCO Health Services Committee (HSC) convened an Expert Panel consisting of experts in clinical medicine and research relevant to VTE in patients with cancer including medical and surgical oncology. Academic and community practitioners, an oncology fellow, and a patient representative were also part of the Panel. The Panel members are listed in the Appendix.

LITERATURE REVIEW AND ANALYSIS

Literature search strategy. An exhaustive systematic literature review was performed of randomized clinical trials (RCTs) examining the efficacy and safety of anticoagulation therapy in patients with cancer regarding survival, bleeding complications, and the prevention of VTE. The comprehensive search included the following electronic databases through the end of 2006: MEDLINE, EMBASE, Cancerlit, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effect, and National Guideline Clearing House. Conference proceedings were searched from 2003 to 2006 (ASCO, American Society of Hematology, International Society of Thrombosis and Hemostasis). References from included articles, relevant excluded reports, and guidelines were searched by hand. In addition, the VTE Panel and other experts from North America and Europe were asked to review identified articles to ensure completeness and provide unpublished results. The literature search had no language restrictions. Subject headings and keywords used in the search process included four major categories, including medical subject headings and text words: venous thromboembolism; anticoagulation including vitamin K antagonists, unfractionated heparin (UFH), and low molecular weight heparin (LMWH); and all malignancies including solid tumors and hematologic malignancies. For RCTs, the recommended search strategy from the Cochrane Collaboration was used.[59,60] These three major search categories were combined by the Boolean "AND." The terms utilized within these major search categories were combined by the Boolean "OR."

Inclusion and exclusion criteria. Included studies had to be RCTs of adult patients with cancer randomly assigned to anticoagulation drug therapy or an appropriate control group. Anticoagulation had to

be with LMWH, UFH, or an oral vitamin K antagonist. Studies were only included if they had VTE or mortality as a priori planned primary or secondary outcomes and described a method of regular patient follow-up to ensure a consistent and identical identification of the outcomes in both study arms. VTE had to be confirmed objectively. Studies were excluded if they were nonrandomized reports, post hoc subgroup analyses, or if they included only patients who did not have cancer. Given the substantial clinical differences, studies of thrombosis prophylaxis related to indwelling catheters were not included in this analysis. Among duplicate publications only the most recent or the most complete report was included.

Data extraction. Two reviewers extracted the data independently on basic study design, patient characteristics, study outcomes, and measures of study quality. Any discrepancies between reviewers were resolved by consensus. Data for analysis were abstracted systematically from the published reports and included authors and citation; category, general type, and stage of malignancy and other demographic patient characteristics; drugs, doses, and schedule of anticoagulation therapy and concomitant interventions; study design (eg, the type of control group [placebo *v* nonplacebo], appropriate description of randomization, blinding, concealment of therapy, description of patient withdrawals or dropouts, power calculations, and intention to treat analysis); and number of patients initially randomly assigned, the number of patients assessable, and the cumulative proportion experiencing specific outcomes.

Study quality. Overall study quality was evaluated by the method of Moher et al.[61] This scale represents a validated instrument for assessing the quality of RCTs. It evaluates study quality based on appropriate methods of randomization, appropriate description of blinding and treatment concealment, and appropriate description of study withdrawals or dropouts. The possible scoring range is from 0 to 5, with poor quality represented by a score of 2 or less.

CONSENSUS DEVELOPMENT BASED ON EVIDENCE

The entire Panel met twice; additional work on the guideline was completed through a steering group. The purposes of the Panel meetings were to refine the questions addressed by the guidelines and to make writing assignments for the respective guideline sections. All members of the Panel participated in the preparation of the draft guideline document, which was then disseminated for review by the entire Panel. Feedback from external reviewers was also solicited. The content of the guidelines and the manuscript were reviewed and approved by the HSC and by the ASCO Board of Directors before dissemination.

GUIDELINE AND CONFLICTS OF INTEREST

All members of the Expert Panel complied with ASCO policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

REVISION DATES

At annual intervals, the Panel Co-Chairs and two Panel members designated by the Co-Chairs will determine the need for revisions to the guidelines based on an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revised guidelines to the HSC and the ASCO Board for review and approval.

RESULTS

SUMMARY OF LITERATURE SEARCH RESULTS

While a limited number of meta-analyses of the value of anticoagulation in patients with cancer have been conducted, most have been limited in their methodology, including poor search and selection strategies, and inclusion of subgroup analyses of the study population with cancer.[62] Even meta-analyses used to support other clinical guidelines often fail to meet criteria for being truly systematic or of reasonable quality based on Quality of Reporting of Meta-Analyses (QUORUM) criteria.[63] The ACCP Conference on Antithrombotic and Thrombolytic Therapy uses a grading system reflecting the perceived strength of the recommendations.[64] Unfortunately, such guidelines only provide limited information on cancer-associated thrombosis.

Primary prophylaxis. Only three studies of a primary prophylaxis strategy in ambulatory patients with cancer have had VTE as a primary outcome and no meta-analysis of this issue has been completed.

Secondary prophylaxis. The comparative impact of LMWH versus vitamin K antagonists on recurrence of VTE specifically in patients with cancer has been studied in four RCTs, all showing a trend toward a lower risk of recurrent VTE for LMWH.[65-68] The comparative impact on cancer-specific mortality of anticoagulants given for VTE has been studied in a number of RCTs, including post hoc analyses of cancer subgroups. A meta-analysis of these studies has been reported by Conti et al.[69] These investigators found no significant different in cancer mortality in eight RCTs that compared LMWH and vitamin K antagonists for all patients (odds ratio [OR] = 0.95; 95% CI, 0.73 to 1.23) or limited to patients with cancer (OR = 0.96; 95% CI, 0.73 to 1.25). None of these studies was designed to study cancer-specific mortality. In another meta-analysis of RCTs of VTE patients comparing LMWH and UFH, Hettiarachchi et al[70] reported a lower 3-month mortality for the subgroup of patients with cancer treated with LMWH compared with those receiving UFH (OR = 0.61; 95% CI, 0.40 to 0.93). Similar results were reported by an earlier meta-analysis.[71]

Surgical prophylaxis. A large number of RCTs of prophylactic anticoagulation have been performed in the perioperative and postoperative setting, although few have addressed outcomes specifically in a cancer population. Smorenberg et al[72] found that, despite a reduction in 3-year mortality in four retrospective studies of prophylactic UFH in resectable GI cancer (OR = 0.65; 95% CI, 0.51 to 0.84), a significant increase in 3-year mortality was found in two prospective RCTs among similar patients (OR = 1.66; 95% CI, 1.02 to 2.71). A recent review of DVT prophylaxis, including subgroup analysis of patients with cancer undergoing surgical procedures, identified 26 studies.[73] A significant reduction in DVT was observed in patients

receiving LMWH, whereas no difference was observed between LMWH and UFH. A meta-analysis of RCTs of prolonged LMWH compared with no postoperative prophylaxis in cancer patients undergoing abdominal surgery was reported by Rasmussen et al.[74,75] The most recent of these meta-analyses identified four RCTs comparing LMWH prophylaxis strategies. Patients receiving LMWH for 4 to 5 weeks after surgery experienced a significantly reduced risk of venographically detected DVT (relative risk [RR] = 0.44; 95% CI, 0.28 to 0.70; $P = .0005$) but not symptomatic VTE (RR = 0.35; 95% CI, 0.06 to 2.22; $P = .27$) compared with those receiving a shorter course.[75] An individual patient data meta-analysis of the two studies of the LMWH tinzaparin confirmed a reduction in risk with extended prophylaxis.[76]

Anticoagulation as cancer treatment. A number of RCTs of anticoagulation treatment in patients with cancer without a diagnosis of VTE addressed overall or cancer-specific mortality as a primary outcome. No significant impact on 1-year mortality of vitamin K antagonists administered in patients with cancer without VTE was found in a meta-analysis including 1,443 patients in nine disease groups from five separate studies (OR = 0.89; 95% CI, 0.70 to 1.13). However, this meta-analysis was not based on a comprehensive systematic review, it allowed trials in the analysis with a combination of anticoagulants, and it did not address the impact of bleeding complications.[72] Another meta-analysis by the same authors explored the impact of UFH on survival in patients with cancer.[62] Only one study was identified as an RCT that studied UFH for more than 7 days.[77] Two other RCTs investigated UFH given via portal vein infusion continuously for 7 days and found a detrimental effect for UFH compared with control (OR = 1.66; 95% CI, 1.02 to 2.71).[78,79] In a recently reported meta-analysis, anticoagulation in patients with cancer without recognized VTE was found to decrease 1-year overall mortality significantly, with an RR of 0.905 (95% CI, 0.847 to 0.967; $P = .003$).[80] The RR for mortality was 0.877 (95% CI, 0.789 to 0.975; $P = .015$) with LMWH, compared with RR = 0.942 (95% CI, 0.854 to 1.040; $P = .239$) with warfarin. Major bleeding episodes occurred less frequently in LMWH patients than in patients receiving warfarin ($P < .0001$).

PREVIOUS GUIDELINES AND CONSENSUS STATEMENTS

ACCP. The ACCP published an evidence-based guideline on antithrombotic and thrombolytic therapy, including chapters on the prevention and treatment of VTE.[55,81,82] This guideline addresses the broad range of patient indications for the prevention and treatment of VTE, but did not focus specifically on the cancer patient, although selected issues related to patients with cancer were discussed. The current ASCO initiative focuses on the specific issues arising in the patient with cancer, including some new issues that have emerged since the last published ACCP guideline. This provides an opportunity to consider some of these issues in greater detail and provide updated recommendations; it is, therefore, complementary to the effort of the ACCP.

National Comprehensive Cancer Network. The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 20 leading National Cancer Institute–designated cancer centers that develops and disseminates clinical practice guidelines in oncology. The NCCN VTE Panel was convened in 2005 and its guidelines were presented in March 2006. The current version of the recommendations on VTE management (version 2.2006) can be found at http://nccn.org/professionals/physician_gls/PDF/vte.pdf.

Italian Guidelines. Since 2004, the Italian Association of Medical Oncology has published online recommendations to direct the clinical practice of Italian oncologists in the management of VTE in patients with cancer. These recommendations are amended annually and were most recently published in English in 2006.[83] The levels of evidence are provided according to a five-point rating system, and the strength of recommendations is assessed on the basis of their relative benefits and risks. The guideline recommendations are comprehensive and focus on six different aspects, including VTE associated with occult cancer, prophylaxis of VTE in cancer surgery, prophylaxis of VTE during chemotherapy or hormonal therapy, prophylaxis of VTE associated with central venous catheters, treatment of VTE in patients with cancer, and anticoagulation and prognosis of cancer.

GUIDELINE RECOMMENDATIONS

1. SHOULD HOSPITALIZED PATIENTS WITH CANCER RECEIVE ANTICOAGULATION FOR VTE PROPHYLAXIS?

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

Literature review and analysis. The reported frequency of VTE in hospitalized patients with cancer has varied widely, with reported incidences ranging from 0.6% to 18% (Table 2).[9,15,22,23,85] Patients at particularly high risk for VTE include older patients, patients with cancers of the brain, pancreas, GI tract, ovary, kidney, bladder, lung, and the hematologic malignancies; patients with metastatic disease; and immobilized, neutropenic, and infected patients. Three double-blind, placebo-controlled, multicenter studies of pharmacologic thromboprophylaxis with either LMWH or fondaparinux in acutely ill hospitalized patients have been reported (Table 3).[86-88] The three studies differed in their inclusion criteria and patients with cancer constituted only a minority of the enrolled participants. Although each study reported a statistically significant reduction in VTE with pharmacologic prophylaxis, only one study provided outcome data for the cancer subset, which was not statistically significant.[85,89] Previous studies on medical prophylaxis using UFH 5000 IU given twice daily in acutely ill medical patients failed to demonstrate a significant reduction in fatal PE.[90] However, other studies utilizing UFH tid (5,000 IU) have indicated efficacy equivalent to LMWH.[91] Analysis of the PREVENT trial data showed that asymptomatic proximal DVT was associated with an increased mortality rate.[87] Although none

Reference	No. of Hospitalizations or Patients	VTE Events No.	VTE Events %
Levitan et al[22]*	1,211,944	7,238	0.6
Sallah et al[23]	1,041	81	7.8
Stein et al[9]	40,787,000	837,000	2
Khorana et al[15]†	66,106	5,272	5.4
Khorana et al[84]	1,015,598	41,666	4.1

Table 2. Frequency of Venous Thrombosis in Hospitalized Patients With Cancer

*Medicare claims data base only includes patients age ≥ 65 years.
†Included only patients with cancer with neutropenia.

Table 3. Trials of Anticoagulants for VTE Prophylaxis in Acutely Ill Hospitalized Medical Patients

Reference	Total No. of Patients	Cancer Patients		Placebo Events		Treatment Events		Relative Risk	P	95% CI
		No.	%	No.	%	No.	%			
MEDENOX[85,86,89]	579*	72	12.4	43/288	14.9	16/291	5.5	0.37	< .001	0.22 to 0.63
				8/41†	19.5	3/31†	9.7			
PREVENT[87]	3,706	190	5.1	73/1,473	4.96	42/1,518	2.77	0.55	.0015	0.38 to 0.8
ARTEMIS[88]	849‡	131	15.4	34/323	10.5	18/321	5.6	0.47	.029	0.08 to 0.69

Abbreviations: VTE, venous thromboembolism; MEDENOX, Prophylaxis in Medical Patients with Enoxaparin; PREVENT, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial; ARTEMIS, ARixtra for ThromboEmbolism Prevention in a Medical Indications Study.
*MEDENOX included a 20-mg enoxaparin arm of 287 patients with event rates equivalent to placebo. Number includes only placebo and patients receiving 40-mg treatment.
†Number of patients with cancer treated with placebo and 40-mg treatment arms. Nonstatistical difference $P = .4$.
‡Total patients assessable for safety analysis; only 644 patients were assessable for primary end point.

of the deaths was considered related to VTE, one third of the deaths were due to cancer, suggesting that asymptomatic VTE in the patients with cancer in this study, most likely, was associated with advanced malignancy.[92]

The 2004 ACCP guidelines strongly recommend (1A) pharmacologic prophylaxis with either low-dose heparin or LMWH for bedridden patients with active cancer.[55] It should be noted that these recommendations are based on clinical trials in which only a minority of enrollees were patients with cancer. However, even in the absence of clear treatment data in hospitalized patients with cancer, the low complication rates observed with prophylaxis in the major medical trials appear to justify the use of pharmacologic prophylaxis in hospitalized patients with cancer. However, none of the randomized studies discussed here has reported bleeding data specifically in the subgroup of patients with cancer (Table 4).

2. SHOULD AMBULATORY PATIENTS WITH CANCER RECEIVE ANTICOAGULATION FOR VTE PROPHYLAXIS DURING SYSTEMIC CHEMOTHERAPY?

Recommendations

(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. Until such time as data are available from RCTs, LMWH or adjusted-dose warfarin (international normalized ratio [INR] ~1.5) is recommended in myeloma patients 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.*

(3) RCTs evaluating antithrombotic agents are needed in patients with multiple myeloma receiving thalidomide or lenalidomide plus chemotherapy and/or dexamethasone.

(4) Research identifying better markers of ambulatory patients with cancer most likely to develop VTE is urgently needed.

Literature Review and Analysis

Low-dose warfarin. There are few data available on the prevention of VTE in ambulatory patients with cancer. In one study, Levine et al[93] showed that low-dose warfarin is effective in reducing the rate of thrombosis during chemotherapy. In a double-blind randomized

trial, 311 patients with metastatic breast cancer were given either very low dose warfarin (1 mg for 6 weeks followed by adjusted dose to a target INR of 1.3 to 1.9) or placebo while receiving chemotherapy. The rate of thrombosis was 0.65% in the warfarin arm and 4.4% in the placebo arm, a statistically significant 85% risk reduction in the rate of VTE with no increase in bleeding. On the basis of these results, the number of patients needed to treat to avoid one event is 23.

LMWH. European investigators recently presented data in abstract form from two double-blind, placebo-controlled, RCTs (TOPIC-1 and TOPIC-2) in patients with metastatic breast cancer (n = 353) or stage III or IV non–small-cell lung carcinoma (n = 547).[94] Patients were randomly assigned to receive either 6 months of the LMWH certoparin (3,000 anti-factor Xa units daily) or placebo for primary prevention of chemotherapy-associated VTE.[94] Patients were screened for DVT by ultrasonography every 4 weeks while on study. In patients with breast cancer, there was no observed difference in the rates of VTE (4%), whereas rates of major bleeding complications during 6 months of treatment were 1.7% for the LMWH arm and 0% for the placebo arm. In patients with lung cancer, there was a nonsignificant trend toward effectiveness of LMWH prophylaxis, with VTE rates of 4.5% for the LMWH arm and 8.3% for the placebo arm ($P = .07$). Major bleeding in patients with lung cancer occurred in 3.7% of the LMWH treated patients versus 2.2% in the placebo group. In a post hoc analysis, rates of VTE in patients with stage IV lung cancer who received LMWH were 3.5% compared with 10.1% for those receiving placebo ($P = .03$). Certoparin is not currently available in the United States.

Thalidomide and derivatives. Routine use of prophylaxis in ambulatory patients with cancer receiving chemotherapy is not recommended because of conflicting data from clinical trials, concern about bleeding, the need for laboratory monitoring and dose adjustment, and the relatively low incidence of VTE. However, the risk of VTE in patients receiving thalidomide has been found to range from 17% to 26% in combination with dexamethasone,[10,28] and from 12% to 28% in combination with other chemotherapy agents including anthracyclines.[29,30] Recent nonrandomized studies of thalidomide-containing regimens in patients with multiple myeloma have suggested efficacy for prophylactic anticoagulation with LMWH,[95,96] warfarin 1 mg[95] and 1.25 mg,[97] and aspirin.[98] Rajkumar et al[99] reported the results of a phase II trial of lenalidomide (an analog of thalidomide) plus dexamethasone in 34 patients with myeloma. Patients received either 80 or

Table 4. Regimens for Prophylaxis/Treatment of VTE in Patients With Cancer

Management	Drug	Regimen*	Estimated Weekly Cost†	Estimated 6-Month Cost†
Prophylaxis				
Hospitalized medical or surgical cancer patients‡	Unfractionated heparin	5,000 U every 8 hours§	$12.08	$313.95
	Dalteparin	5,000 U daily	$152.40	$3,962.50
	Enoxaparin	40 mg daily	$154.59	$4,019.29
	Fondaparinux‖	2.5 mg daily	$199.92	$5,197.92
Treatment of established VTE				
Initial¶	Dalteparin#	100 U/kg every 12 hours	$426.73	NA
		200 U/kg daily**	$426.73	NA
	Enoxaparin#	1 mg/kg every 12 hours	$541.06	NA
		1.5 mg/kg daily**	$405.79	NA
	Heparin	80 U/kg IV bolus, then 18 U/kg/h IV (adjust level based on PTT†)	$24.99	NA
	Fondaparinux#	< 50 kg, 5.0 mg daily	$399.84	NA
		50-100 kg, 7.5 mg daily	$599.76	NA
		> 100 kg, 10.0 mg daily	$799.68	NA
	Tinzaparin	175 U/kg daily	$198.17	NA
Long term‡	Dalteparin	200 U/kg daily for 1 month; then 150 U/kg daily	$334.12	$8,687.04
	Warfarin	5-10 mg PO daily; adjust dose to INR 2-3	$4.43	$115.15

NOTE. Relative contraindications to anticoagulation include, among other conditions: 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), and epidural catheter placement. Dalteparin (Fragmin; Eisai Inc, Woodcliff Lake, NJ); Enoxaparin (Lovenox; sanofi aventis, Bridgewater, NJ); Fondaparinux (Arixtra; GlaxoSmithKline, Brentford, United Kingdom); Tinzaparin (Innohep; Pharmion, Boulder, CO).

Abbreviations: VTE, venous thromboembolism; IV, intravenously; NA, not available; PTT, partial thromboplastin time; LMWH, low molecular weight heparin; PO, orally; INR, international normalized ratio; CMS, Centers for Medicare and Medicaid Services; FUL, Federal Upper Limit.

*All subcutaneously except as indicated.

†Cost considerations for estimates provided. (1) Cost for injectable drugs is based on Medicare Part B price list effective September 30, 2006 (with no administration fees or other adjustments). (2) Cost estimates for warfarin do not include additional costs for frequent monitoring required to maintain INR in acceptable range. (3) Calculations assume a 70-kg patient. (4) Long-term therapy with dalteparin was calculated as follows: 6-month costs calculated with 1-month start-up + 5-month maintenance. Weekly costs estimated by dividing 6-month cost by 26 weeks. (5) Oral warfarin costs represent ambulatory oral prescriptions. These prices were calculated by using CMS published Medicaid FUL prices. Calculations were as follows: assumed a maximum of 90-day prescription for warfarin using FUL prices per tablet plus a typical dispensing fee of $4.50 (90-day prescription estimated to be $57.58). Six-month cost estimate is twice this amount. Weekly cost is estimated by maximum of 90-day prescription for warfarin using FUL prices per tablet plus a typical dispensing fee of $4.50 (90-day prescription estimated to be $57.58). Six-month cost estimate is twice this amount. Weekly cost is estimated by dividing 6-month cost by 26 weeks.

§5,000 U every 12 hours has also been used but appears to be less effective.

‡Duration is for length of hospital stay or until ambulatory.

§5,000 U every 12 hours has also been used but appears to be less effective.

‖Not approved by the US Food and Drug Administration for this indication.

¶For 5-7 days minimum and until INR is in the therapeutic range for 2 consecutive days if changing to warfarin.

#Significant renal clearance; avoid in patients with creatinine clearance 30 mL/min or adjust dose based on anti-factorXa levels.

**Optimal dosing unclear in patients > 120 kg.

††PTT range of 1.5 to 2.5× the control value is commonly used. The best approach is to determine the PTT therapeutic range using the local method to correspond to a heparin level of 0.3 to 0.7 U/mL using a chromogenic Xa assay.

‡‡Total duration of therapy depends on clinical circumstances. Treatment for 6 months or longer is usually needed with active cancer.

325 mg of aspirin daily. Although the observed rate of VTE was lower than in a previous study of lenalidomide plus dexamethasone without aspirin prophylaxis, another trial casts doubt on the efficacy of aspirin as an antithrombotic agent in this population.[100,101] Although similar concerns have arisen with novel antiangiogenic agents such as bevacizumab, the available data on the risk of thrombosis are contradictory, although a consistent increase in bleed risk has been encountered.[11,31,102,103]

3. SHOULD PATIENTS WITH CANCER UNDERGOING SURGERY RECEIVE PERIOPERATIVE VTE PROPHYLAXIS?

Recommendations

(1) All patients undergoing major surgical intervention for malignant disease should be considered for thromboprophylaxis.

(2) 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 a high risk of bleeding or active bleeding.

(3) Prophylaxis should be commenced preoperatively, or as early as possible in the postoperative period.

(4) 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.

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

(6) 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 previous history of VTE.

Literature Review and Analysis

Risk of VTE in surgery. VTE is a common complication in cancer surgical patients.[104] The presence of malignant disease doubles the risk for DVT,[105] with reported incidences of asymptomatic calf vein thrombi at 40% to 80%, proximal-vein thrombi 10% to 20%, PE 4% to 10%, and fatal PE 1% to 5% without perioperative thromboprophylaxis.[55] Factors influencing the risk of VTE in this setting include advanced age (OR = 2.6), higher stage of disease (OR = 2.7), increasing duration of anesthesia (OR = 4.5), prolonged postoperative immobilization (OR = 4.4), and previous history of VTE (OR = 6.0).[32] Up to one fourth of symptomatic thromboembolic events occur after discharge and require readmission to the hospital.[106] Importantly, in an observational study, 40% of VTE events occurred 21 days after surgery and VTE was responsible for 46% of deaths within 30 days after surgery.[32] All patients undergoing major surgical intervention for malignant disease (laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes) are considered at high risk for the development of VTE. On the other hand, surgery for malignant disease is associated with a greater frequency of bleeding complications, and need for blood transfusion independent of the type of prophylaxis employed.[95] An assessment of the risk of postoperative bleeding is based on several surgical considerations, including the extent of dissection and the adequacy of intraoperative hemostasis.

VTE prophylaxis in the surgical setting includes mechanical and pharmacologic methods. Mechanical methods overcome venous stasis either passively with graduated compression stockings, or actively with intermittent pneumatic calf compression (IPC) or mechanical foot pumps. Pharmacologic methods of thromboprophylaxis include UFH, LMWHs, fondaparinux (an indirect inhibitor of activated factor Xa), and the vitamin K antagonists.

Mechanical prophylaxis. Recent pooled analyses of studies of all three mechanical methods of thromboprophylaxis, evaluated in different patient populations, indicate that these methods employed as monotherapy for VTE prevention reduce the frequency of DVT by 66%, but only achieve a modest and insignificant reduction of 31% in the frequency of PE.[97] In a small study, 355 patients were randomly assigned to calf compression or control in trials that reported results for patients with cancer alone.[98] Rates of DVT decreased from 21% (control) to 12.8% with IPC. Pneumatic calf compression for 5 days has been shown in controlled trials to be of value in reducing VTE in both gynecologic malignancies and intracranial surgery. Its value in reducing VTE in gynecologic malignancy has been demonstrated in a controlled trial in which DVT rates decreased from 34.6% to 12.7% ($P < .005$).[107] Venous thrombosis detected by radioactive fibrinogen uptake decreased from 18.4% to 1.9% ($P = .0051$) in 102 patients undergoing craniotomy for brain tumor, subarachnoid hemorrhage, or subdural hematoma.[108]

UFH. Low-dose UFH has been evaluated extensively for both the prevention of postoperative DVT and fatal PE.[50] Low-dose UFH is administered in a dose of 5,000 units, commencing 2 hours before operation, and continued every 8 hours subcutaneously after surgery. In cancer surgery patients it reduces DVT rates from 22% in controls to 9%.[109] In a meta-analysis of 10 trials with 919 patients with cancer, low-dose UFH prophylaxis reduced DVT rates from 30.6% in the control group to 13.6% in those receiving the active treatment ($P < .001$).[98] Low-dose UFH is also effective in the prevention of PE, including in those whose operation is undertaken for cancer. Among a subgroup of 953 patients with cancer randomly assigned to low-dose

heparin or control arms in the International Multicenter Trial, low-dose UFH prophylaxis reduced the frequency of PE from 0.8% in the control group to 0.1% in the UFH group.[50]

LMWH. Studies comparing the effects of LMWH and UFH on DVT rates in patients with cancer indicate broadly similar prophylactic efficacies for these two agents.[110-112] In a large randomized study of more than 600 assessable patients undergoing planned curative abdominal or pelvic surgery for cancer, enoxaparin 40 mg daily and UFH 5,000 U tid were found to be equally efficacious in reducing VTE, with no differences in bleeding events or other complications.[111] In a large meta-analysis of available randomized trials comparing LMWH, UFH, and placebo or no treatment, LMWH appeared to be as safe and effective as UFH in reducing VTE, in both the general population and a large subgroup of patients with cancer.[91] Another study compared 2,500 *v* 5,000 U of LMWH in 2,000 patients who underwent surgery, 65% of whom underwent laparotomy for cancer.[112] DVT rates decreased from 14.9% in those receiving 2,500 U to 8.5% in those receiving 5,000 U ($P = .001$). This study is the first to demonstrate that increasing the dose of LMWH can improve its thromboprophylactic efficacy in patients with cancer without increasing bleeding complications.[112] Potential advantages favoring LMWHs over UFH in cancer surgery prophylaxis include once-daily versus tid injections and a lower risk of heparin-induced thrombocytopenia.

Fondaparinux. Fondaparinux was found to be at least as effective as dalteparin in preventing VTE in an RCT of high-risk abdominal surgery patients.[32] Nearly 68% of the 2,048 patients enrolled onto this study had cancer. A post hoc analysis suggested improved efficacy in reducing VTE for fondaparinux versus dalteparin in this large subgroup of patients with cancer.

Combined prophylaxis. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients. A Cochrane review of 19 studies showed that low-dose UFH combined with graduated compression stockings was four times more effective for VTE prevention than low-dose UFH alone.[113]

Prolonged prophylaxis. Two recent randomized studies suggest that prolonging the duration of prophylaxis up to 4 weeks is even more effective than shorter duration therapy in reducing postoperative VTE.[114,115] In an RCT, VTE rates were 4.8% in patients receiving enoxaparin for 4 weeks after surgery for abdominal or pelvic cancer versus 12% in patients receiving enoxaparin for 1 week after surgery ($P = .02$).[114] In a second randomized study, patients undergoing major abdominal surgery were randomly assigned to receive 4 weeks versus 1 week of dalteparin prophylaxis. VTE rates were 16.3% in the 1-week arm compared with 7.3% in the 4-week prophylaxis arm ($P = .012$).[115] More than half of patients in each arm in this second study underwent cancer surgery. There was no increase in bleeding complications associated with prolonged prophylaxis in either study.

Specific surgical populations. Laparoscopic surgery. There are limited data regarding the benefit of thromboprophylaxis in patients undergoing laparoscopic surgery. There are no prospective studies in cancer-specific populations. In a large retrospective study in patients with prostate cancer undergoing laparoscopic radical prostatectomy, the rate of symptomatic VTE was low (0.5%).[116] In the absence of prospective data, however, standard prophylactic regimens may be tailored to individual patient risk factors.

Neurosurgery. A randomized trial of 307 patients undergoing neurosurgical procedures showed a significant reduction in VTE with

LMWH and graduated compression stockings combined compared with compression stockings alone.[117]

Gynecologic oncology. Patients with gynecologic malignancies constitute a high-risk subgroup of surgical patients with cancer and have been studied specifically in clinical trials of both pharmacologic and mechanical thromboprophylaxis. In an RCT involving 185 patients undergoing operation for gynecologic malignancy, 13 of 88 patients (14.8%) receiving low-dose UFH every 12 hours and 12 of 97 patients (12.4%) in the control arm developed VTE, with no significant difference in the incidence of proximal DVT, calf vein thrombosis, or PE.[118] However, another study showed that low-dose UFH administered every 8 hours and started before surgery reduced the DVT rate to 4% compared with 19% in the control arm ($P < .001$).[119]

IPC was equally effective but with no significant complications such as bleeding.[119] In a study of patients with gynecologic malignancies undergoing surgery, IPC devices were placed intraoperatively and continued for 5 days.[107] IPC use was associated with a three-fold reduction in VTE. Advantages of IPC devices include safety, ease of use, and lower cost than pharmacologic methods.[120] Two RCTs and a large retrospective series have found the incidence of VTE to be 1% to 6.5% in a gynecologic oncology patient population treated with low-dose UFH, LMWH, or IPC.[119-121] When used during and after major gynecologic surgery, IPC may be as effective as low-dose UFH and LMWH in reducing DVT; unfortunately, most studies have included a small number of patients and these studies have not shown efficacy in lowering the incidence of PE or mortality.[120-122] A more intensive prophylaxis regimen consisting of higher or more frequent doses of low-dose UFH or LMWH may be considered in patients with risk factors for IPC failure when used alone, such as age older than 60 years or prior VTE.[120] Although data are limited in the gynecologic literature on the benefits of using a combination of mechanical and pharmacologic prophylaxis, presence of two of three identified risk factors for failing IPC (age > 60 years, cancer, prior VTE) places patients in the highest risk category for the development of VTE.[120] A combined approach seems appropriate in the highest-risk patients, and is recommended by the Seventh ACCP Consensus Conference.[55]

4. WHAT IS THE BEST TREATMENT FOR PATIENTS WITH CANCER WITH ESTABLISHED VTE TO PREVENT RECURRENT VTE?

Recommendations

(1) LMWH is the preferred approach for the initial 5 to 10 days of anticoagulant treatment of the cancer patient 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 to 3 are acceptable for long-term therapy when LMWH is not available.

(3) 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) 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.

(5) 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, pre-existing bleeding diathesis such as thrombocytopenia (platelet count $< 50,000/\mu L$) or coagulopathy.

(6) For elderly patients, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring and dose adjustment is necessary to avoid excessive anticoagulation and further increase in the risk of bleeding.

Literature Review and Analysis

Anticoagulant therapy is the preferred approach for most patients with the available agents for VTE prophylaxis and treatment summarized in Table 4 along with estimated costs. However, individual patients may require other modalities, including thrombolysis, thromboembolectomy, and/or placement of an IVC filter. The indications for the use of these additional modalities are essentially the same as for patients who do not have cancer.[82] Systemic thrombolysis is indicated in selected patients with life-threatening PE, and thrombolysis is indicated for selected patients with massive or nonresolving ileo-femoral thrombosis.

Monotherapy with LMWH. LMWH given for 3 to 6 months is more effective than vitamin K antagonists for preventing recurrent VTE.[67,123] The risks of LMWH therapy include bleeding complications and osteoporosis. RCTs indicate that the rates of major and overall bleeding with LMWH regimens given for 3 to 6 months are similar to those for patients receiving UFH or LMWH followed by oral vitamin K antagonist therapy.[65,67,123] Heparin-induced thrombocytopenia and clinically relevant osteoporosis occurred uncommonly. Treatment with subcutaneous LMWH should be given for at least 6 months.[67] Indefinite treatment should be considered for selected patients with active cancer, such as those with metastatic disease and those receiving chemotherapy, because cancer is a strong continuing risk factor for recurrent VTE. The relative benefits and risks of continuing LMWH beyond 6 months, versus switching to oral vitamin K antagonist therapy, remains a clinical judgment in the individual patient in the absence of clinical trials data. Future studies to evaluate this are necessary.

The CLOT (Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) study is the largest reported RCT comparing LMWH with vitamin K antagonist therapy in patients with cancer with VTE.[67] Patients with cancer who had acute, symptomatic proximal DVT, PE, or both, were randomly assigned to receive LMWH (dalteparin 200 IU/kg of body weight subcutaneously once daily for 5 to 7 days) followed by a coumarin derivative for 6 months, or dalteparin alone for an extended period (6 months at 200 IU/kg of body weight once daily for 1 month followed by 150 IU/kg body weight once daily for 5 months). During the 6-month study period, symptomatic, objectively documented recurrent VTE occurred in 27 of 336 patients in the dalteparin-alone group (9%) and in 53 of 336 patients (17%) in the vitamin K antagonist group ($P = .002$), a relative risk reduction of 49%.[67] Major bleeding occurred in 6% in the dalteparin-alone group and in 4% in the vitamin K antagonist group (not statistically

significant), and corresponding rates of any bleeding were 14% and 19%, respectively.

In the Longitudinal Investigation of Thromboembolism Etiology study, among 200 patients with cancer and acute symptomatic proximal-vein thrombosis observed for 1 year, recurrent VTE occurred in 16 of 100 (16%) patients who received intravenous UFH followed by vitamin K antagonists for 3 months, compared with seven of 100 patients (7%) treated initially and for 3 months with the LMWH tinzaparin (175 U/kg once daily).[124]

In a randomized, open-label multicenter trial, subcutaneous enoxaparin sodium (1.5 mg/kg once a day) was compared with warfarin given for 3 months in 146 patients with VTE and cancer.[65] Of the 71 assessable patients assigned to receive warfarin, 15 patients (21.1%) experienced one major outcome event defined as major bleeding or recurrent VTE within 3 months compared with seven patients (10.5%) of the 67 assessable patients assigned to receive enoxaparin ($P = .09$). There were six deaths as a result of hemorrhage in the warfarin group compared with none in the enoxaparin group. In an RCT of 122 patients with cancer with acute symptomatic VTE randomly assigned to subcutaneous enoxaparin for up to 180 days versus enoxaparin as initial therapy followed by warfarin, no significant differences in major and minor bleeding rates between treatment groups were reported.[125] The US Food and Drug Administration recently approved dalteparin sodium for extended treatment of symptomatic VTE to reduce the risk of recurrence of VTE in patients with cancer.[125a]

Recurrent VTE. Among patients with recurrent VTE despite adequate anticoagulant therapy, the management options include treatment with an alternate anticoagulant regimen (ie, LMWH if the patient had received a vitamin K antagonist) or inserting a vena cava filter. The vena cava filter may be effective for preventing clinically important PE, but data in a cancer-specific population are lacking.[126] In an 8-year follow-up report of the only randomized study of permanent vena cava filters in the general population, the use of filters reduced the risk of PE, but increased that of DVT and had no effect on survival.[127] Although less of a concern among patients with extensive cancer and limited life expectancy, consideration should be given to continuing an effective anticoagulant regimen, if it appears safe to do so, to prevent morbidity from recurrent venous thrombosis. The role of removable vena cava filters remains uncertain because of a lack of RCTs evaluating their effectiveness and clinical outcomes. Studies evaluating the use of retrievable filters and the need for concomitant anticoagulant therapy are warranted.

Intracranial malignancy. Patients with cancer with intracranial tumors are at increased risk for thrombotic complications. Anticoagulant therapy is absolutely contraindicated in patients with active intracranial bleeding. In addition, caution is indicated in patients with recent intracranial surgery and those at high risk for falls, pre-existing bleeding diathesis, or poor compliance with medical therapy. However, the presence of an intracranial tumor or brain metastases without evidence of active bleeding is not an absolute contraindication to anticoagulation. Limited data are available regarding the safety and efficacy of antithrombotic therapy in patients with primary or metastatic tumors of the brain who develop concurrent venous thrombosis.[128-133] A high failure rate has been reported with IVC filters, without improved overall survival or reduced intracranial hemorrhage in small retrospective series.[128-130] Dose-adjusted UFH and warfarin have been shown to effectively reduce the risk of VTE without

an increase in rates of intracranial bleeding or death and few reported recurrent thromboses.[128,130-133]

Elderly patients. Elderly patients frequently have concurrent cancer and thrombosis, given that both entities increase with age.[134] In a large observational study of consecutive patients with VTE, including patients with cancer, fatal bleeding occurred in 0.8% and 0.4% of older and younger patients, respectively (hazard ratio = 2.0; 95% CI, 1.2 to 3.4).[135] In addition, death from PE occurred in 3.7% of older patients compared to 1.1% for the younger subjects (hazard ratio = 3.6; 95% CI, 2.7 to 4.7). The risk of death due to PE exceeded the incidence of fatal bleeding.[135] The risk of falls should be considered when anticoagulating an elderly cancer patient.

5. SHOULD PATIENTS WITH CANCER RECEIVE ANTICOAGULANTS IN THE ABSENCE OF ESTABLISHED VTE TO IMPROVE SURVIVAL?

Recommendations

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

(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 Review and Analysis

Tumor cells express tissue factor and other procoagulants, and tumors interact with the endothelium, leukocytes, and platelets during invasive growth, dissemination, and formation of metastases. Inhibiting the hemostatic system with UFH or LMWH may alter the biology of cancer and improve survival independent of any direct effect on VTE. Two types of studies have evaluated the value of anticoagulants in patients with cancer as measured by survival in those treated with UFH, LMWH, or vitamin K antagonists.

Evidence from VTE treatment studies. In the first type of trial, patients with cancer with VTE were treated with anticoagulants primarily to prevent recurrent thrombosis, and the effect on survival was a secondary end point. In a retrospective subgroup analysis of a small number of patients with cancer with proximal DVT, those treated with LMWH had a 6-month mortality rate of 7% (one in 15) v 44% (eight in 18) of those treated with UFH ($P = .02$).[136] Meta-analyses of trials that compared initial VTE therapy with UFH versus LMWH confirmed a survival benefit in patients with cancer randomly assigned to LMWH.[70,71,137,138] Among nine RCTs, a subgroup analysis of 629 patients with cancer revealed 46 deaths in the LMWH group versus 71 deaths in the UFH group during 3 months of follow-up, for an OR of 0.61 (95% CI, 0.40 to 0.93) in favor of LMWH; this was not attributed to either fatal bleeding or PE. In the CLOT study, overall survival as a secondary outcome was not significantly improved with long-term treatment with an LMWH (dalteparin), compared with short-term treatment with dalteparin followed by long-term treatment with a vitamin K antagonist in patients with cancer with VTE.[139] However, a post hoc analysis of 150 patients with nonmetastatic disease showed a 12-month survival of 36% in the long-term dalteparin group versus 20% in the short-term dalteparin plus vitamin K antagonist group ($P = .04$). This finding is limited by its post hoc nature, potential imbalance of important prognostic features, and the small number of patients with nonmetastatic disease. These data are provocative but none of these studies was specifically designed to determine the effect of LMWH on survival, and all analyses were performed post hoc.

Evidence from survival studies. Warfarin. The second type of study tested anticoagulants in patients with cancer without thrombosis, with survival as the primary end point. Zacharski et al[140] randomly assigned patients with lung, colon, head and neck, or prostate cancer to standard anticancer therapy versus standard therapy plus warfarin for an average of 26 weeks. There was no difference in overall survival between the two groups. However, among 50 patients with small-cell lung cancer, significant improvements in time to disease progression and in overall survival were observed with warfarin compared with no anticoagulation. In a subsequent study of 328 patients with small-cell lung cancer randomly assigned to chemotherapy alone or to chemotherapy plus warfarin, disease-free survival and overall survival were not statistically improved, although there was a trend favoring warfarin treatment.[141] In a Cancer and Leukemia Group B study evaluating warfarin with chemotherapy and radiation therapy in patients with limited-stage small-cell lung cancer, no significant differences were observed in overall, failure-free, or disease-free survival, or in patterns of relapse between the two groups.[142]

UFH. A study of 277 patients with small-cell lung cancer randomly assigned to chemotherapy with or without subcutaneous UFH for 5 weeks reported better complete response rates (37% v 23%; P = .04), median survival (317 v 261 days; P = .01), and overall survival rates at 1, 2, and 3 years among those receiving UFH.[77] A subsequent subset analysis showed that the benefit was greater in patients with less extensive disease.

LMWH. In a recent study of 84 patients with small-cell lung cancer randomly assigned to chemotherapy alone or chemotherapy plus dalteparin at a dose of 5,000 U once daily for 18 weeks of chemotherapy, median progression-free survival of 6 and 10 months (P = .01) and median overall survival of 8 and 13 months (P = .01) were reported in those receiving chemotherapy alone versus chemotherapy plus dalteparin, respectively.[143] In summary, studies in small-cell lung cancer combining warfarin and chemotherapy and the limited data with UFH or LMWH combined with chemotherapy are of interest but inadequate to base a recommendation upon at this time.

Several other RCTs have evaluated the impact of LMWH therapy on survival in patients with cancer without thrombosis. Kakkar et al[144] conducted an RCT in 385 patients with advanced malignancy assigned to receive either once-daily dalteparin or placebo for 1 year in addition to standard therapy. Although no significant difference in survival was observed overall between the two groups at 1, 2, and 3 years, a post hoc analysis suggested an improved survival with dalteparin in the group of 102 patients who had a better prognosis and were alive 17 months after random assignment. In a study of 304 patients with advanced solid tumors receiving a LMWH (nadroparin), or placebo for 6 weeks with standard therapy, median survival was improved with LMWH (8.0 v 6.6 months; P = .021) with a hazard ratio for survival at 1 year of 0.75 (95% CI, 0.59 to 0.96).[145] In a study of 141 patients with advanced breast, colon, lung, or prostate cancer randomly assigned to receive standard therapy alone or in combination with dalteparin daily, no difference in any outcome measures were observed between the two groups, although the small sample size may have led to the study being underpowered.[146]

In a recent meta-analysis of the efficacy and safety of anticoagulation in patients with cancer without recognized VTE, 11 RCTs were identified.[80] Anticoagulants, most notably LMWH, were found to significantly improve overall survival while increasing the risk for

bleeding complications. The authors conclude, based on the limitations of the available data, that the use of anticoagulants in patients with cancer without VTE with the intention of improving survival cannot currently be recommended. Major limitations of the studies include the use of post hoc and subgroup analyses, the heterogeneous patient populations studied, the multiple treatment strategies used, and the small number of patients studied. A significant effect of vitamin K antagonists on survival is unlikely. The impact of anticoagulation on the survival of patients with cancer remains uncertain and warrants further study.

LIMITATIONS OF THE EVIDENCE AND DIRECTIONS FOR FUTURE RESEARCH

Patients with cancer represent a high-risk population for VTE and associated complications including early mortality. The effective and safe prevention of VTE in this population is a laudable goal but remains a challenge in terms of both treatment-associated toxicities and variable evidence from clinical trials, in addition to meta-analyses of such trials. The guideline presented here offers explicit recommendations for the use of anticoagulation and other measures for the prevention of VTE in hospitalized patients with cancer, those receiving cancer chemotherapy on an ambulatory basis, patients with cancer in the perioperative and postoperative period, those with recent prior VTE, and finally, for patients with cancer without an established VTE as a possible adjunct to cancer therapy. Nevertheless, the available data addressing these and related issues are limited. There remains a considerable need for additional research, particularly in the form of large, well-designed, randomized, controlled clinical trials. Systematic reviews and meta-analyses of clinical trials serve a useful purpose in systematically searching for the totality of evidence and, when appropriate, combining the results of smaller and often inconclusive trials. Nevertheless, the quality and validity of meta-analyses are only as valid as those of the individual clinical trials included. Table 5 provides a summary of the Panel Recommendations for VTE.

Prophylaxis in the Various Clinical Settings Considered

Hospitalized patients with cancer should be considered candidates for VTE prophylaxis in the absence of specific contraindications such as active bleeding. As noted above, the recommendations for VTE prophylaxis in hospitalized patients with cancer are based on clinical trials that enrolled, in most cases, only a small proportion of patients with cancer. Although the low complication rates with prophylaxis in the major medical trials appear to justify the use of VTE prophylaxis in hospitalized patients with cancer, none of the randomized studies reported bleeding data specifically in the subgroup of patients with cancer. There are few data available on the prevention of VTE in ambulatory patients with cancer. Although the guideline recommends the use of LMWH or adjusted-dose warfarin in patients receiving thalidomide with chemotherapy or dexamethasone at recognized high risk for VTE, the recommendation is based on nonrandomized studies and extrapolation from randomized studies in other similar high-risk settings. Additional studies are needed to evaluate further the potential risk of VTE and the value of primary prophylaxis in patients receiving novel targeted therapies, particularly the class of antiangiogenic agents. All patients undergoing major surgical intervention for malignant disease should be considered for thromboprophylaxis for at least 7 to 10 days postoperatively. Although prolonged

	Table 5. Summary Recommendations and Evidence	
Patient Group	Role of VTE Prophylaxis	Evidence
Hospitalized patients with cancer	Patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants (UFH, LMWH, or fondaparinux) in the absence of bleeding or other contraindications to anticoagulation.*	Multiple RCTs of hospitalized medical patients with subgroups of patients with cancer. The 2004 ACCP guidelines strongly recommend (1A) prophylaxis with either low-dose heparin or LMWH for bedridden patients with active cancer.
Ambulatory patients with cancer without VTE receiving systemic chemotherapy	Routine prophylaxis with an antithrombotic agent is not recommended except as noted below.	Routine prophylaxis in ambulatory patients receiving chemotherapy is not recommended due to conflicting trials, potential bleeding, the need for laboratory monitoring and dose adjustment, and the relatively low incidence of VTE.
	LMWH or adjusted-dose warfarin (INR ~1.5) is recommended in myeloma patients on thalidomide or lenalidomide plus chemotherapy or dexamethasone.	This recommendation is based on nonrandomized trial data and extrapolation from studies of postoperative prophylaxis in orthopedic surgery and a trial of adjusted-dose warfarin in breast cancer.
Patients with cancer undergoing surgery	All patients undergoing major surgical intervention† for malignant disease should be considered for thromboprophylaxis with low-dose UFH, LMWH, or fondaparinux starting as early as possible for at least 7-10 days unless contraindicated.*	RCTs of UFH and those comparing the effects of LMWH and UFH on DVT rates in patients with cancer indicate broadly similar prophylactic efficacies for these two agents.[50,110-112]
	Mechanical methods may be added to anticoagulation in very high risk patients but should not be used alone unless anticoagulation is contraindicated.*	A Cochrane review of 19 studies.[113]
	LMWH for up to 4 weeks may be considered after major abdominal/pelvic surgery with residual malignant disease, obesity, and a previous history of VTE.	Recent RCTs suggest that prolonging prophylaxis up to 4 weeks is more effective than short-course prophylaxis in reducing postoperative VTE.[114,115]
Treatment of patients with established VTE to prevent recurrence	LMWH is the preferred approach for the initial 5-10 days in cancer patient with established VTE.	LMWH for 3 to 6 months is more effective than vitamin K antagonists given for a similar duration for preventing recurrent VTE.[67,123]
	LMWH for at least 6 months is preferred for long-term anticoagulant therapy. Vitamin K antagonists with a targeted INR of 2-3 are acceptable when LMWH is not available. The CLOT study demonstrated a relative risk reduction of 49% with LMWH v a vitamin K antagonist.[67] Dalteparin sodium approved by the FDA for extended treatment of symptomatic VTE to reduce risk of recurrence of VTE in patients with cancer (FDA 2007).	
	Anticoagulation for an indefinite period should be considered for patients with active cancer (metastatic disease; continuing chemotherapy).	In the absence of clinical trials, benefits and risks of continuing LMWH beyond 6 months is a clinical judgment in the individual patient. Caution is urged in elderly patients and those with intracranial malignancy.
	Inferior vena cava filters are reserved for those with contraindications to anticoagulation or PE despite adequate long-term LMWH.	Consensus recommendation due to lack of data in cancer-specific populations.
Anticoagulants in the absence of established VTE to improve survival	Anticoagulants are not currently recommended to improve survival in patients with cancer without VTE.	RCTs and meta-analyses of warfarin, UFH, and LMWH have reported encouraging but variable results generally showing clinical benefit only in subgroup analyses.[80]

Abbreviations: VTE, venous thromboembolism; UFH, unfractionated heparin; LMWH, low molecular weight heparin; RCT, randomized controlled trial; ACCP, American College of Chest Physicians; INR, international normalized ratio; DVT, deep venous thrombosis; PE, pulmonary embolism; CLOT, Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer; FDA, US Food and Drug Administration.
*Relative contraindications to anticoagulation include, among other conditions: 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) and epidural catheter placement.
†Laparotomy, laparoscopy, or thoracotomy lasting > 30 minutes.

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 obesity, residual cancer, or a previous history of VTE, additional studies are needed to better define the comparative benefits and risks associated with prolonged anticoagulation. LMWH is the preferred approach for both initial and long-term anticoagulant therapy for documented VTE in patients with malignant disease. Al-

though indefinite anticoagulant therapy should be considered for patients with active cancer, including those with metastatic disease or those continuing to receive systemic chemotherapy, this recommendation was based on Panel consensus in the absence of clinical trials data. Additional clinical studies are needed to evaluate the comparative benefits and harms of extended VTE prophylaxis in high-risk patients, including the elderly and those with CNS malignancies.

Finally, anticoagulation cannot currently be recommended to improve survival in patients with cancer without established VTE. However, the results of individual clinical trials and meta-analyses provide conflicting data, which require further investigation. Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.

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Appendix