Cancer and thrombosis: implications of published guidelines for clinical practice

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Cancer is a frequent finding in patients with thrombosis, and thrombosis is much more prevalent in patients with cancer, with important clinical consequences. Thrombosis is the second most common cause of death in cancer patients. Venous thromboembolism (VTE) in cancer is also associated with a high rate of recurrence, bleeding, a requirement for long-term anticoagulation, and worsened quality of life. Risk factors for cancer-associated VTE include particular cancer types, chemotherapy (with or without antiangiogenic agents), the use of erythropoietin-stimulating agents, the presence of central venous catheters, and surgery. Novel risk factors include platelet and leukocyte counts and tissue factor. A risk model for identifying cancer patients at highest risk for VTE has recently been developed. Anticoagulant therapy is safe and efficacious for prophylaxis and treatment of VTE in patients with cancer. Available anticoagulants include warfarin, heparin, and low-molecular weight heparins (LMWHs). LMWHs represent the preferred therapeutic option for VTE prophylaxis and treatment. Their use may be associated with improved survival in cancer, although this issue requires further study. Despite the significant burden imposed by VTE and the availability of effective anticoagulant therapies, many oncology patients do not receive appropriate VTE prophylaxis as recommended by practice guidelines. Improved adherence to guidelines could substantially reduce morbidity, decrease resource use, enhance quality of life, and improve survival in these patients.

Key words: anticoagulant, cancer, heparins, thromboembolism, thrombosis, warfarin

Introduction

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the second leading cause of death in hospitalized and ambulatory cancer patients [1–3]. Compared with patients who do not have cancer, oncology patients are at substantially higher risk for new and recurrent VTE [4–7]. The risk of VTE in cancer patients is particularly increased for those who are undergoing surgery (three- to fivefold) [2], those who are receiving chemotherapy (6.5-fold) [6], those who carry certain genetic mutations [8], and those with previous DVT [9]. The increased risk of recurrent VTE in cancer patients is greatest in the first few months after malignancy is diagnosed [8] and can persist for many years after an initial episode of symptomatic DVT [9].

VTE may itself be a sign of occult malignancy [10, 11]. In a series of patients hospitalized for bilateral DVT, 25% were known to have cancer at admission, and new cancer was diagnosed in 26% of those without known cancer at admission [10]. Of note, 62% of the known cancers and 70% of the new cancers had already metastasized. The odds of cancer in this series were nearly five times higher for patients with idiopathic thrombosis than for those with secondary thrombosis [10].

VTE also adversely affects quality of life. In a study assessing the effect of VTE on the Short Form-36 physical component summary (PCS) and mental component summary scores, the mean PCS scores among patients with VTE were lower than those in the general population at baseline, 1 month, and 4 months [12]. In fact, the mean PCS scores were lower in these patients at 1 month than in patients who have arthritis or chronic lung disease.

Given that patients requiring treatment for DVT are often hospitalized initially, the management of DVT also adds considerably to healthcare resource use [13]. Early or late complications of VTE can extend the hospital stay by 7–11 days, adding a mean $1784 (2002 USD) per day to hospitalization costs [13]. Costs associated with bleeding complications of DVT are particularly high: a mean hospital stay of 18 days and hospital costs of $43 187 (2002 USD) [13].

Acknowledging the significant impact of VTE, the American Society of Clinical Oncology (ASCO) [14], the American College of Chest Physicians (ACCP) [15], and the National Comprehensive Cancer Network (NCCN) [16] have all recently issued clinical practice guidelines for the prevention and treatment of cancer-associated thrombosis. Despite these
mechanisms and risk factors for cancer-associated thrombosis

hemostasis, tissue factor, and angiogenesis

The hemostatic system is known to influence tumor angiogenesis, which is critical to the growth of solid tumors [20]. In particular, the expression of tissue factor (TF) by tumor or stromal cells results in a generally procoagulant tumor microenvironment [21]. TF expressed in this manner is a procoagulant and can directly activate factor X; TF released by monocytes or macrophages can induce activation of factor VII [22].

TF also may stimulate angiogenesis both directly, by means of signaling through cytoplasmic tails, and indirectly, through generation of thrombin and interaction with protease-activated receptors. In a recent retrospective analysis, TF was expressed in both noninvasive and invasive pancreatic neoplasms, but not in normal pancreatic cells [23]. TF expression in cancer cells was correlated with expression of vascular endothelial growth factor and increased microvessel density, which suggested linkage with angiogenesis. More important, VTE was significantly more frequent among patients with high levels of TF expression in resected tumor specimens than among those with low levels (26.3% versus 4.5%; P = 0.04) [23]. High levels of TF expression have also been shown to predict poor prognosis in patients with ovarian [24] and pancreatic cancers [25].

anticancer therapies

Many common antineoplastic treatment modalities carry an increased risk of thrombotic events. Large population-based studies involving groups of pooled cancer patients have demonstrated a significantly increased risk in patients undergoing chemotherapy. In a population-based study of patients with a new diagnosis of VTE, there was a significantly increased risk of VTE in those who were receiving chemotherapy [odds ratio (OR) 6.5, confidence interval (CI) 2.11–20] [6]. In a large retrospective cohort of cancer patients, patients receiving chemotherapy were at significantly higher risk for VTE than were patients not receiving chemotherapy (OR 2.3 and 2.0, respectively) [26].

Studies in specific types of cancer and with specific antineoplastic agents have also supported the role of chemotherapy in predicting the risk of cancer-associated VTE. In prospective studies of breast cancer patients, the risk of VTE in patients receiving chemotherapy in addition to tamoxifen or surgery was increased two- to sevenfold [27, 28]. A recent meta-analysis of breast cancer patients revealed that use of adjuvant hormonal therapy was associated with a 1.5- to sevenfold increased risk of VTE [29].

More recently, antiangiogenic agents have been associated with particularly high rates of thrombosis. Thalidomide and lenalidomide do not significantly increase the risk of thrombosis when used alone for the treatment of newly diagnosed or refractory or relapsed multiple myeloma; reported rates of VTE range from 2% to 4% [30, 31]. However, when these agents are combined with steroids, melphalan, doxorubicin, or other chemotherapeutic agents, much higher rates of VTE have been reported, ranging from 8% to 27% [32, 33]. Rates as high as 43% have been reported among adults receiving thalidomide and chemotherapy for renal cell carcinoma [34]. High rates of cancer-associated VTE have also been reported in patients with colon and gastric cancers who are receiving antiangiogenic agents [35–37]. In a recent meta-analysis of clinical trials of bevacizumab in combination with chemotherapy or interferon across a variety of cancers, the use of bevacizumab was associated with a 33% relative increase in the risk of VTE [38]. This finding contradicts that of an earlier pooled analysis of clinical trials [39]. However, the later meta-analysis included a larger study population, and its findings were consistent with data from nonrandomized studies of bevacizumab and with the known increased risk of VTE associated with antiangiogenic inhibitors as a class. This increased risk of VTE must be considered in the context of the known increased risk of serious bleeding events with bevacizumab. The risk–benefit ratio of prophylaxis for patients receiving bevacizumab will have to be evaluated in a prospective clinical study before changes in clinical practice can be recommended [39].

The mechanisms behind the risk of thromboembolic events with these treatment strategies are poorly understood. Many of these therapies do induce vascular damage, either directly or indirectly, thereby promoting local activation of the coagulation process.

risk factors for cancer-associated thrombosis

Potential risk factors for VTE can be divided into patient-, cancer-, and treatment-related characteristics [40]. Patient-related factors include advanced age, female sex, black ethnicity, comorbid conditions, and prothrombotic mutations. Tumor-related factors relate to the site, stage, and duration of cancer. Treatment-related factors include both pharmacologic agents [e.g. chemotherapeutic agents, hormonal agents, antiangiogenic agents, and erythropoiesis-stimulating agents (ESAs)] and mechanical causes, e.g. surgery and central venous catheters (CVCs)]. Most recently, the predictive relationship between cancer-related thrombosis and biomarkers has been investigated, with pretreatment platelet and leukocyte counts showing promise as predictors, in addition to TF expression,
inflammatory status as measured by C-reactive protein, and markers of platelet activation [40].

Recently, a predictive model was shown to discriminate between outpatients with a low, intermediate, or high risk of chemotherapy-associated thrombosis (Table 1) [41]. The final model, which had a C-statistic of 0.7 for both the test (n = 2701) and validation (n = 1365) cohorts, included five variables: (i) high-risk cancer site (two points for very high-risk sites and one point for high-risk sites); (ii) platelet count ≥350 000/mm³; (iii) hemoglobin concentration <10 g/dl, or use of ESAs, or both; (iv) leukocyte count >11 000/mm³; and (v) body mass index ≥35 kg/m² (one point for each). In the validation cohort, the incidence of VTE over a median 2.5 months of follow-up was 0.3% among patients with a score of 0, 2% among those with a score of 1 or 2, and 6.7% among those with a score of 3 or higher [41]. Such a model might be used to identify patients who are clinically at high risk for VTE. The National Heart, Lung, and Blood Institute has recently funded a prophylaxis study for cancer outpatients identified as high risk on the basis of this predictive model.

**prevention and treatment of VTE in cancer patients**

**general considerations: warfarin**

For >50 years, warfarin anticoagulation has been a standard treatment for prophylaxis and treatment of VTE. For treatment of VTE, it has typically been given after initial therapy with unfractionated heparin (UFH) or, more recently, a low-molecular weight heparin (LMWH) [42]. Although efficacious, warfarin has several important limitations to its use. The first is that its dosing can be difficult, particularly because of its slow onset (the anticoagulant effect may not reach its peak until after 72–96 h) and slow clearance from the body (duration of action, 2–5 days) [43]. Warfarin use also can be a burden to patients. The most recent guidelines for management of VTE from the NCCN recommend dosing of long-term warfarin therapy to achieve a target international normalized ratio (INR) of 2.0–3.0 [16]. Thus, patients must undergo frequent blood sampling in an attempt to maintain adequate, but not excessive, dosing.

Achievement of the target INR with oral warfarin may be more difficult in cancer patients than in those without cancer [44], especially in view of the anorexia and emesis common in patients with cancer [45, 46]. Cancer patients require frequent interruption of anticoagulation for procedures, which further compounds the difficulty of warfarin dose management. In one large randomized trial, the INR was within the target range in the warfarin group only 46% of the time [47]. Even when the INR is within the target range, however, VTE can still occur [4]. Cancer is often suspected as a contributing cause in such cases of ‘warfarin failure’ [48].

Furthermore, interactions between chemotherapeutic agents, particularly 5-fluorouracil (5-FU)-based regimens and warfarin, can add to the difficulty associated with maintaining a therapeutic INR. A study assessing changes in the INR and bleeding in cancer patients given minidose warfarin during treatment with 5-FU-based regimens found a high incidence of INR abnormalities and bleeding [49]. Another study in patients with advanced cancer found a significant pharmacokinetic interaction between capetitbine and warfarin, resulting in exaggerated anticoagulant activity [50].

With warfarin treatment, as with all anticoagulant treatments, there is an increased risk of bleeding, which may be particularly pronounced in patients with cancer [4, 51]. In a retrospective analysis of patients enrolled in two randomized trials of UFH versus LMWH followed by warfarin treatment, the risk of major bleeding was six times higher in patients with cancer [51]. Moreover, the increased risk among cancer patients did not appear to relate to the INR. Indeed, bleeding complications occurred most often among patients in the lowest INR category (INR ≤ 2.0) [51].

Finally, the anticoagulant effects of warfarin may be influenced by interactions with nutrients and herbal preparations as well [43]. Together, these factors can make the use of warfarin therapy particularly challenging for clinicians and patients in the oncologic setting.

**general considerations: UFH**

UFH has been used for >40 years in the prevention and treatment of VTE. The heparin species contain a pentasaccharide sequence, which binds to antithrombin and enhances heparin’s ability to inhibit both thrombin and factor Xa. UFH can be given either s.c. or i.v., and its effects can be reversed with protamine sulfate. A potential complication associated with UFH administration is the development of heparin-induced thrombocytopenia [52].

Subcutaneous low-dose UFH is commonly used for thromboprophylaxis in medical and surgical cancer patients. A meta-analysis of 29 trials of surgical patients who received UFH, 919 of whom had cancer, showed a significant reduction

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**Table 1. Predictive model for calculating risk of chemotherapy-associated thrombosis**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Odds ratio (95% CI)</th>
<th>VTE risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>4.3 (1.2–15.6)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)</td>
<td>1.5 (0.9–2.7)</td>
<td>1</td>
</tr>
<tr>
<td>Low risk (breast, colorectal, head and neck)</td>
<td>1.0 (reference)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count ≥350 000/mm³</td>
<td>1.8 (1.1–3.2)</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level &lt;10 g/dl or use of red cell growth factors</td>
<td>2.4 (1.3–4.2)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count &gt;11 000/mm³</td>
<td>2.2 (1.2–4)</td>
<td>1</td>
</tr>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>2.5 (1.3–4.7)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Shown are multivariate analysis-identified variables independently associated with the risk of VTE and corresponding risk scores calculated on the basis of the risk model [41].

CI, confidence interval; VTE, venous thromboembolism; BMI, body mass index.
in the incidence of VTE, from 30.6% in the group not receiving prophylaxis to 13.3% in the UFH group [53]. Another meta-analysis of heparin studies in medical patients showed 56% and 58% risk reductions in the incidence of DVT and clinical PE, respectively, in the heparin group versus the control group (P < 0.001) [54].

general considerations: LMWHs
LMWHs were developed to overcome some of the limitations of UFH—namely, the variable anticoagulant effects, the low bioavailability, the need for frequent monitoring, the longer time of onset, and the variable pharmacokinetics [55]. Because warfarin has known limitations as well (described previously), especially for patients with cancer, the role of LMWHs in long-term anticoagulant treatment also has been investigated.

Compared with UFH, LMWHs have more predictable pharmacokinetics and greater bioavailability. Thus, a weight-adjusted dose of a LMWH can be given by s.c. injection once or twice daily without laboratory monitoring in most patients [55]. These agents have been shown to be safe and efficacious in numerous clinical situations and are recommended by the ACCP for thromboprophylaxis in moderate- and high-risk surgical patients [15], for postdischarge prophylaxis in high-risk surgical patients (including those who have undergone cancer surgery) [15], for initial short-term treatment of DVT in general patient populations [55], and for the first 3–6 months of long-term anticoagulation in patients with DVT and cancer [55]. The drawbacks of LMWHs include the need for daily injection, with the attending risk of local injury, and the higher direct costs, although overall costs are lower with LMWHs than with UFH because LMWHs can be administered at home [55].

prophylaxis of VTE in hospitalized patients with cancer
In randomized trials of VTE prophylaxis in various populations of patients with cancer, the rates of VTE and DVT generally have been significantly lower with LMWHs than with UFH or placebo, without a significant increase in major bleeding (Table 2) [56–63]. In these trials, the benefit of the LMWHs appeared to be related to both the dose and the duration of treatment [59, 60]. Three studies have assessed the benefits of LMWHs in medical patients, although patients with malignancies constituted only a minority of those enrolled [61, 63, 64]. Each study reported a significant reduction in VTE with LMWH compared with placebo; however, only one provided efficacy data for the cancer subset. The reduction in the incidence of VTE in this substudy was not statistically significant [7, 62].

The low bleeding rates observed with LMWH prophylaxis in the three major medical trials strongly argue for pharmacologic prophylaxis in hospitalized patients with cancer [61, 63, 64]. Unfortunately, none of these studies has published bleeding rates specifically for the cancer subgroups of their populations.

Both the ASCO and NCCN guidelines support the use of pharmacologic VTE prophylaxis in hospitalized cancer patients unless one or more contraindications to prophylactic anticoagulation are present. According to the ASCO guidelines, relative contraindications to anticoagulation include active, uncontrollable bleeding; active cerebrovascular hemorrhage; dissecting or cerebral aneurysm; bacterial endocarditis; pericarditis, active peptic or other gastrointestinal ulceration; severe, uncontrolled, or malignant hypertension; severe head trauma; pregnancy (for warfarin); heparin-induced thrombocytopenia; and epidural catheter placement [14].

According to the NCCN guidelines, relative contraindications include recent central nervous system bleed; intracranial or spinal lesions at high risk for bleeding; active bleeding (more than two units transfused in 24 h); chronic, clinically significant measurable bleeding (>48 h); thrombocytopenia (<50 000/mm³); severe platelet dysfunction; recent operation at high risk for bleeding; underlying coagulopathy [clotting factor abnormalities or lengthening of prothrombin time or activated partial thromboplastin time]; spinal anesthesia or lumbar puncture; and high risk for falls [16].

Although both the ASCO and NCCN recommend VTE prophylaxis for cancer patients throughout the duration of hospitalization, cancer patients are known to remain at risk for VTE after hospital discharge. The NCCN guidelines acknowledge that the risk of VTE is sufficiently high in some medical and surgical oncology patients to warrant extended VTE prophylaxis in the outpatient setting [16]. Based on data from two large studies of prolonged prophylaxis in the surgical setting, the ASCO guidelines recommend that prophylaxis for up to 4 weeks be considered in patients undergoing major abdominal or pelvic surgery for cancer who have risk factors for VTE (e.g. a residual tumor after operation, obesity, or a history of VTE) [57, 60].

prophylaxis of VTE in ambulatory patients with cancer
Subgroups of ambulatory cancer patients may have rates of VTE as high as those in hospitalized medical or surgical patients. Indeed, owing to shifts in the care of cancer patients from the hospital setting to the ambulatory setting, a high percentage of VTE events currently occur in the outpatient setting. Prophylaxis may therefore be beneficial in such groups. In the earliest randomized study of VTE prophylaxis in ambulatory cancer patients, low-dose warfarin or placebo was administered to 311 women receiving therapy for metastatic breast cancer [65]. There were seven events in the placebo group, but only one in the warfarin group [relative risk reduction (RRR) 85%; P = 0.03]. Unfortunately, subsequent trials have failed to confirm the benefit of prophylaxis in the ambulatory setting. The TOPIC-1 and TOPIC-2 studies evaluated LMWH prophylaxis in patients with metastatic breast cancer (n = 353) and patients with stage III or IV non-small-cell lung carcinoma (n = 547), respectively [66]. Patients were randomly assigned to receive either certoparin (3000 U daily) or placebo for 6 months, and all underwent screening ultrasonography every 4 weeks. Over the 6 months of treatment, the rates of major bleeding complications in breast cancer patients were 1.7% in the LMWH arm and 0% in the placebo arm. The rates of major bleeding complications in lung cancer patients were 3.7% in the LMWH arm and 2.2% in the placebo arm. LMWH showed a nonsignificant trend toward effectiveness, with a VTE rate of 4.5% among lung cancer patients, compared with 8.3% for placebo (P = 0.07). Similar
Table 2. Studies of venous thromboembolism prophylaxis in patients with cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up</th>
<th>Population</th>
<th>Interventions</th>
<th>VTE</th>
<th>Major bleeding</th>
<th>Mortality</th>
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<tbody>
<tr>
<td><strong>Surgical patients</strong></td>
<td></td>
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<tr>
<td>Bergqvist et al. [56]</td>
<td>2070</td>
<td>30 days</td>
<td>Elective abdominal surgery for cancer</td>
<td>Dalteparin 5000 IU q.d., dalteparin 2500 IU q.d.</td>
<td>8.5%&lt;sup&gt;a&lt;/sup&gt;, 14.9%; P &lt; 0.001</td>
<td>4.6%&lt;sup&gt;a&lt;/sup&gt;, 3.6%; P = NS</td>
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<td></td>
<td></td>
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<td>(66.4% of patients had surgery as result of a malignant disorder)</td>
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<tr>
<td>ENOXACAN [57]</td>
<td>631</td>
<td>3 months</td>
<td>Elective cancer surgery</td>
<td>Enoxaparin 40 mg q.d., UFH t.i.d.</td>
<td>14.7%, 18.2%</td>
<td></td>
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<tr>
<td>McLeod et al. [58]</td>
<td>475</td>
<td>10 days</td>
<td>Partial or total bowel resection</td>
<td>Enoxaparin 40 mg q.d., heparin 5000 U t.i.d.</td>
<td>13.9%, 16.9%; P = 0.052</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bergqvist et al. (ENOXACAN II) [59]</td>
<td>332</td>
<td>31 days, 3 months</td>
<td>Planned surgery for abdominal or pelvic cancer</td>
<td>Enoxaparin 40 mg q.d. × 6–10 days, then enoxaparin 40 mg q.d. or placebo × 19–21 days</td>
<td>E/E 4.8%, E/P 12%, P = 0.02; E/E 5.5%, E/P 13.8%, P = 0.01</td>
<td>E/E 0.8%, E/P 0.4%, P &gt; 0.99; E/E 1.2%, E/P 0.4%, P = 0.62</td>
<td></td>
</tr>
<tr>
<td>Rasmussen et al. (FAME) [60]</td>
<td>198&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 weeks</td>
<td>Major abdominal surgery for cancer</td>
<td>Dalteparin 5000 IU q.d. × 1 week, dalteparin 5000 IU q.d. × 4 weeks</td>
<td>19.6%&lt;sup&gt;a&lt;/sup&gt;, 8.8%; P = 0.03</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Medical patients</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>ARTEMIS 2006 [61]</td>
<td>849</td>
<td>6–14 days</td>
<td>Immobilized medical inpatients</td>
<td>Fondaparinux 2.5 mg q.d. × 14 days, placebo × 6–14 days</td>
<td>5.6%, 10.3%; P = 0.029</td>
<td>0.2%, 0.2%</td>
<td>3.3%, 6%</td>
</tr>
<tr>
<td>MEDENOX 2003 [62]</td>
<td>118&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6–14 days</td>
<td>Immobilized medical inpatients</td>
<td>Enoxaparin 40 mg q.d. × 6–14 days, placebo × 6–14 days</td>
<td>9.7%, 19.5%; P = 0.4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PREVENT 2004 [63]</td>
<td>3706</td>
<td>21 days</td>
<td>Immobilized medical inpatients</td>
<td>Dalteparin 5000 IU q.d. × 14 days, placebo × 14 days</td>
<td>2.77%, 4.96%; P = 0.0015</td>
<td>0.49%, 0.16%</td>
<td>2.35%, 2.32% (day 21)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Rates shown are for deep vein thrombosis.

<sup>b</sup>Rates shown are for any bleeding.

E/E, enoxaparin followed by enoxaparin; E/P, enoxaparin followed by placebo; q.d., each day; t.i.d., three times daily; NR, not reported; NS, not significant; UFH, unfractionated heparin; VTE, venous thromboembolism.
trials in patients with glioma also have not shown thromboprophylaxis to be beneficial [67].

Results from the PROTECHT study, a large Italian study of prophylaxis in the ambulatory setting, were recently presented [68]. The study randomly assigned >1100 cancer patients undergoing chemotherapy to receive either nadroparin (3800 IU s.c. once daily) or placebo. Prophylaxis began at the initiation of chemotherapy and lasted throughout chemotherapy treatment or up to 4 months. At the 12-month follow-up, fewer thromboembolic events had occurred in the nadroparin arm than in the placebo arm (2.0% versus 3.9%). Furthermore, patients with lung or pancreatic cancer were more likely to experience thromboembolic events than were patients with breast, gastrointestinal, ovarian, or head and neck cancers, which suggested that these patient groups may benefit from LMWH prophylaxis. Given the conflicting data from clinical trials and the known risk of bleeding in the cancer population, prophylaxis is not currently recommended even for high-risk ambulatory cancer patients, although these recommendations may change as new data emerge.

One exception to this policy is the high-risk ambulatory group comprising patients with multiple myeloma who are receiving thalidomide- or lenalidomide-based combination therapy. The current consensus, based on nonrandomized studies, is that all newly diagnosed patients treated with thalidomide- or lenalidomide-containing regimens should receive thromboprophylaxis [14, 16]. Fixed low-dose warfarin (1–2 mg) has been modestly effective at decreasing VTE rates in patients receiving thalidomide with dexamethasone but has been ineffective in patients receiving thalidomide with chemotherapy [33, 69]. The use of prophylactic LMWH has been shown to eliminate the excess VTE risk resulting from adding thalidomide to doxorubicin-containing chemotherapy regimens [33, 70]. Unfortunately, phase III studies have not been carried out in this setting.

treatment of VTE in patients with cancer

Several studies have addressed treatment of VTE in patients with cancer (Table 3) [47, 71–75]. To date, the CLOT (Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) study, which compared dalteparin with vitamin K antagonist (VKA) therapy, is the largest randomized trial of VTE treatment in patients with cancer (n = 672) [47]. This study reported a 52% RRR in the incidence of recurrent VTE in favor of dalteparin: during the 6-month study period, 27 of 336 patients in the dalteparin group had recurrent VTE versus 53 of 336 patients in the VKA group (P = 0.002) (Table 3) [47]. No significant differences in the rates of major bleeding or any bleeding were observed between the two groups. Dalteparin is currently the only LMWH approved by the United States Food and Drug Administration for extended treatment of symptomatic VTE to reduce the recurrence of VTE in patients with cancer.

Three additional studies assessed the use of LMWH for extended VTE treatment in patients with cancer. The CANTHANOX (Secondary Prevention Trial of Venous Thrombosis with Enoxaparin) study compared 3 months of

<table>
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<tr>
<th>Study</th>
<th>Follow-up</th>
<th>Population</th>
<th>Agents</th>
<th>VTE</th>
<th>Major bleeding</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charbonnier et al. (FRAXODI) [71]</td>
<td>3 months</td>
<td>Proximal DVT</td>
<td>Nadroparin b.i.d., nadroparin q.d.</td>
<td>7.2%a, 4.1%a</td>
<td>1.2%, 1.3%</td>
<td>NR</td>
</tr>
<tr>
<td>Merli et al. [72]</td>
<td>3 months</td>
<td>Symptomatic DVT</td>
<td>Enoxaparin b.i.d., enoxaparin q.d., UFH</td>
<td>6.4%, 12.2%, 6.7%</td>
<td>1.3%, 1.7%, 2.1%</td>
<td>NR</td>
</tr>
<tr>
<td>Meyer et al. [73]</td>
<td>3 months</td>
<td>PE or DVT</td>
<td>Enoxaparin, warfarin</td>
<td>10.9%, 21.1%, 8%</td>
<td>0.09, 16%, P = 0.07</td>
<td>NR</td>
</tr>
<tr>
<td>Lee et al. (CLOT) [47]</td>
<td>6 months</td>
<td>Symptomatic acute DVT</td>
<td>Dalteparin q.d. × 5–7 days + warfarin × 6 months</td>
<td>6%</td>
<td>4%, P = 0.27</td>
<td>NR</td>
</tr>
<tr>
<td>Hull et al. (LITE) [74]</td>
<td>3 months</td>
<td>Symptomatic PE and/or PE</td>
<td>Enoxaparin; UFH</td>
<td>T 7%, W 7%; T 7%, W 7%</td>
<td>T 20%, W 10%; T 7%, W 7%; T 7%, W 7%</td>
<td>T 41%, W 39%; T 7% W 7%</td>
</tr>
<tr>
<td>Deleger et al. (ONEXINOX) [75]</td>
<td>3 months</td>
<td>Symptomatic VTE</td>
<td>Tinzaparin; UFH, enoxaparin; HD enoxaparin; warfarin</td>
<td>T 6.9%; HD 6.3%; W 16%; HD 6.2%; W 16%</td>
<td>T 7%, W 7%; T 7%, W 7%; T 7%, W 7%</td>
<td>T 41%, W 39%; T 7% W 7%</td>
</tr>
</tbody>
</table>

Table 3. Studies of venous thromboembolism treatment in patients with cancer

No significant differences in the rates of major bleeding or any bleeding were observed between the two groups. Dalteparin is currently the only LMWH approved by the United States Food and Drug Administration for extended treatment of symptomatic VTE to reduce the recurrence of VTE in patients with cancer. However, the use of prophylactic LMWH has been shown to eliminate the excess VTE risk resulting from adding thalidomide to doxorubicin-containing chemotherapy regimens [33, 70]. Unfortunately, phase III studies have not been carried out in this setting.
warfarin therapy with 3 months of enoxaparin therapy in patients with malignancy and proximal DVT or PE [73]. Because of slow recruitment, the study was terminated prematurely after 147 patients have been randomly assigned to therapy. At 3 months, seven patients in the enoxaparin group had recurrent VTE or major bleeding (the combined primary end point) versus 15 patients in the warfarin group ($P = 0.09$). Most of the primary outcomes were due to major bleeding (five patients in the enoxaparin group versus 12 in the warfarin group). In the warfarin group, six of the patients died of major bleeding, and at the 6-month follow-up, 31% of patients in the enoxaparin group had died, compared with 38.7% of patients in the warfarin group ($P = 0.25$). These findings suggest that warfarin may be associated with a higher risk of bleeding than LMWH is when used as long-term VTE treatment in patients with cancer [73].

The three-arm ONCENOX (Secondary Prevention Trial of Venous Thrombosis with Enoxaparin) study included 101 patients with cancer and VTE. Because of the small number of patients enrolled, no differences between the enoxaparin and warfarin groups were observed with regard to the incidence of recurrent VTE, major bleeding, or death [75].

The LITE (Long-Term Innohep Treatment Evaluation) study found tinzaparin to be more efficacious than warfarin in 200 patients with cancer [74]. Tinzaparin treatment reduced the rate of recurrent VTE by ~50%; however, the difference was not statistically significant at the end of the 3-month treatment period. There were no differences in bleeding rates between the two groups.

Compared with warfarin, LMWHs generally reduce the overall risk of recurrent VTE when used for the extended treatment of VTE [55, 73–75], a finding confirmed by a recently published Cochrane systematic review [76]. Furthermore, LMWHs do not increase major bleeding rates and appear to be as safe as VKAs. These findings, like those seen in prevention trials, appear to be related to the dose and the duration of therapy.

### long-term central venous catheters and VTE in cancer patients

Rates of DVT among patients with a CVC in place have ranged from 11.7% to 66% [77, 78]. These are higher than the rates reported for mechanical or septic complications of CVCs [77]. The risk of thromboembolic complications appears to peak within 4–8 weeks after CVC placement [77, 78].

In cancer patients, CVCs can be associated with upper limb DVT [79]. Thrombosis tends to develop ipsilaterally to the catheter [77] and may be more prevalent in subclavian veins than in innominate veins or venae cavae [78]. It is noteworthy that most cancer patients with CVC-related thrombosis are not symptomatic [77, 78].

CVC-related DVT can result in significant morbidity and mortality. In a study of 86 consecutive patients with CVC-related DVT, 15% of the patients were considered to have PE [80]. Moreover, two of these patients died despite receiving adequate heparin therapy.

No definite value has been established for prophylaxis of CVC-related thrombosis in cancer patients. Although some studies and meta-analyses have reported a benefit [81, 82], more recent studies have not [83–85]. It may be that the sample sizes of these studies were too small to permit detection of significant differences between treatment groups [85].

### ASCO, NCCN, and ESMO guidelines and impact on clinical practice

Recent guidelines from the ASCO [14], the NCCN [16], and the European Society for Medical Oncology (ESMO) [86] recommend consideration of the use of anticoagulants in the following groups:

- All hospitalized adults (medical or surgical) who have known or suspected cancer, for prophylaxis against VTE [14, 16]. The ESMO guidelines, however, restrict this recommendation of prophylactic anticoagulation to hospitalized cancer patients confined to bed. The ASCO guidelines also call for the prophylactic use of anticoagulants in outpatients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone [14, 86].
- Cancer patients undergoing major cancer surgery. The ESMO guidelines recommend prophylaxis with LMWH or UFH [86].
- Patients with cancer and established VTE, to prevent recurrence of thromboembolic events [14, 16, 86].

In general, unless there is a contraindication, hospitalized patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants (Table 4) [14, 16]. Routine prophylaxis during outpatient chemotherapy is not indicated in most cases [14, 86]. Mechanical techniques for thromboprophylaxis (e.g. graduated compression stockings, intermittent pneumatic calf compression, and mechanical foot pumps) should be the sole method of prophylaxis only when the patient has a contraindication to pharmacologic anticoagulation [14].

For cancer patients with established VTE, initial therapy should consist of either LMWH given for 5–10 days [14, 16] or UFH [86]. LMWH should also be used for long-term therapy (≥6 months) to prevent recurrent VTE. A VKA may be used if LMWHs are not available, with the dosage adjusted to achieve an INR of 2.0–3.0. Indefinite anticoagulant prophylaxis should be considered for high-risk patients, such as those with metastatic disease and those receiving chemotherapy [14, 86]. The ESMO guidelines also recommend both VKAs and LMWHs for treatment of VTE in patients with cancer, giving the two regimens an equal-strength recommendation [86]. A vena cava filter is indicated only for patients with contraindications to anticoagulants or patients with recurrent VTE despite adequate long-term therapy with LMWH [14].

It is worth noting that even though guidelines recommending anticoagulant prophylaxis and treatment have been in place for years, only about half of the candidate patients receive appropriate anticoagulation [17, 18]. Further, oncologists consider routine thromboprophylaxis for only a minority of their patients (<5% in one survey) [19]. Publication of guidelines for thromboprophylaxis, by itself, may not be sufficient to change routine clinical practice;
additional interventions may be necessary [87]. In a study by
Kucher et al. [88], the implementation of a hospital-wide
computer alert program that warned physicians about patients
at risk for DVT increased the use of prophylaxis and
significantly reduced the rates of DVT and PE among
the hospitalized population. In another study, the use of a formal
continuing medical education program for prevention of VTE
did lead to some improvement in adherence, although
prophylaxis remained underused in the participating hospitals
[89]. This same study found that a formal quality assurance
program provided no additional benefit. Clearly, other
educational interventions are required to improve adherence to
thromboprophylaxis guidelines and thereby improve outcomes.

**effects of VTE and cancer on survival**

**relation between cancer and survival after VTE**

Thrombosis has long been known as the second leading cause
of death in cancer patients [90]. VTE is second only to infection
as a cause of death among hospitalized cancer patients,
contributing to as many as 18% of deaths in this population
[1]. One of every seven deaths among hospitalized cancer
patients is related to PE [19]. In one analysis, Medicare patients
who had concurrent VTE and malignancy had a 94% probability of
dying within 6 months, a probability that was
three times higher than that of patients with VTE and no
malignancy [91].

Patients with concurrent VTE and cancer are also at higher
risk for other adverse outcomes. For example, the probability of
readmission for VTE within 6 months was almost four times
higher among Medicare patients with cancer than among
Medicare patients without malignancy [91]. DVT has also been
linked with negative quality-of-life measures in an inpatient
population, of whom 12.5% had active cancer as a risk factor
for VTE [12].

**impact of antithrombotic therapy on survival after VTE in patients with cancer**

Some have speculated that thromboprophylaxis might improve
survival in patients with VTE and cancer. In fact, an early meta-
analysis of 13 randomized trials of VTE treatment (in both
cancer and noncancer populations) found that the relative risk
of mortality was reduced by ∼25% with the use of LMWH as
compared with the use of UFH [92].

To date, four randomized trials have had sufficient statistical
power to detect a significant difference in 1-year survival
between cancer patients who received an LMWH and those
who received placebo or standard treatment (Table 5) [93–96].
Two of these studies showed a significantly longer median
survival time among patients treated with LMWH [94, 95].

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**Table 4. Recommended anticoagulant regimens for venous thromboembolism prophylaxis and treatment in patients with cancer**

<table>
<thead>
<tr>
<th>Management phase</th>
<th>Dosage</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>UFH 5000 U s.c. every 8 h</td>
<td>Significant renal clearance; avoid in patients with creatinine clearance &lt;35 ml/min or adjust dose based on antifactor Xa levels</td>
</tr>
<tr>
<td></td>
<td>Dalteparin 5000 U s.c. daily</td>
<td>Significant renal clearance; avoid in patients with creatinine clearance &lt;35 ml/min or adjust dose based on antifactor Xa levels</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 40 mg s.c. daily</td>
<td>Significant renal clearance; avoid in patients with creatinine clearance &lt;35 ml/min or adjust dose based on antifactor Xa levels</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux 2.5 mg s.c. daily&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Significant renal clearance; avoid in patients with creatinine clearance &lt;35 ml/min or adjust dose based on antifactor Xa levels</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin 4500 U s.c. or 75 U/kg s.c. daily</td>
<td>Significant renal clearance; avoid in patients with creatinine clearance &lt;35 ml/min or adjust dose based on antifactor Xa levels</td>
</tr>
<tr>
<td>Treatment: initial&lt;sup&gt;c&lt;/sup&gt;</td>
<td>UFH 80 U/kg i.v. bolus, then 18 U/kg/h i.v.&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Optimal dosing unclear in patients &gt;120 kg.</td>
</tr>
<tr>
<td></td>
<td>Dalteparin 100 U/kg s.c. every 12 h; 200 U/kg s.c. daily&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Optimal dosing unclear in patients &gt;120 kg.</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 1 mg/kg s.c. every 12 h; 1.5 mg/kg s.c. daily&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Optimal dosing unclear in patients &gt;120 kg.</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux &lt;50 kg: 2.5–5 mg s.c. daily; 50–100 kg: 5–7.5 mg s.c. daily; &gt;100 kg: 7.5–10 mg s.c. daily</td>
<td>Optimal dosing unclear in patients &gt;120 kg.</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin 175 U/kg s.c. daily</td>
<td>Optimal dosing unclear in patients &gt;120 kg.</td>
</tr>
<tr>
<td>Treatment: long term&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Dalteparin 200 U/kg s.c. daily × 1 month, then 150 U/kg s.c. daily</td>
<td>Significant renal clearance; avoid in patients with creatinine clearance &lt;35 ml/min or adjust dose based on antifactor Xa levels</td>
</tr>
<tr>
<td></td>
<td>Warfarin 5–10 mg p.o. daily&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Significant renal clearance; avoid in patients with creatinine clearance &lt;35 ml/min or adjust dose based on antifactor Xa levels</td>
</tr>
</tbody>
</table>

<sup>a</sup>Duration: until ambulatory or until hospital discharge.
<sup>b</sup>Not approved by the U.S. Food and Drug Administration for this indication.
<sup>c</sup>For 5–7 days minimum and until the INR is in the therapeutic range for two consecutive days if changing to warfarin.
<sup>d</sup>Adjust to achieve PTT of 2–2.9 times control value.
<sup>e</sup>Optimal dosing unclear in patients >120 kg.
<sup>f</sup>Duration: minimum 3–6 months for DVT and 6–12 months for PE. LMWH monotherapy is preferred for treatment of proximal DVT or PE and prevention of recurrent VTE in patients with advanced or metastatic cancer.
<sup>g</sup>Adjust dose to achieve INR of 2.0–3.0.

DVT, deep vein thrombosis; INR, international normalized ratio; i.v., intravenously; LMWH, low-molecular weight heparin; PE, pulmonary embolism; p.o., per os (by mouth); PTT, partial thromboplastin time; s.c., subcutaneously; UFH, unfractionated heparin; VTE, venous thromboembolism.

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Adapted from NCCN [16] and Lyman 2007 [14].
Table 5. Survival trials of low-molecular weight heparin in patients with cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up</th>
<th>Population</th>
<th>Agents</th>
<th>VTE</th>
<th>Major bleeding</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kakkar et al. [93]</td>
<td>385</td>
<td>1 year</td>
<td>Advanced malignancy</td>
<td>Dalteparin 5000 IU daily</td>
<td>2.4%; 3.3%</td>
<td>0.5%; 0%</td>
<td>46%; 41%; P = 0.19</td>
</tr>
<tr>
<td>Altinbas et al. [94]</td>
<td>84</td>
<td>1 year</td>
<td>Small-cell lung cancer</td>
<td>Chemotherapy, dalteparin 5000 U daily; chemotherapy alone</td>
<td>0%; 2.5%</td>
<td>0%; 0%</td>
<td>51.3%; 29.5%</td>
</tr>
<tr>
<td>Klerk et al. [95]</td>
<td>302</td>
<td>1 year</td>
<td>Metastasized or locally</td>
<td>Nadroparin (weight based)</td>
<td>1%; 2%</td>
<td>3%; 1%</td>
<td>39%; 27%</td>
</tr>
</tbody>
</table>
| Sideras et al. [96] | 141 | Advanced breast, prostate, lung, colorectal cancer | Dalteparin 5000 IU; placebo/standard care | 69% [a]; 7%                                 | 39% [a]; 7%     | Median time of survival—D: 10.5 (7.6–12.2) months; P = 0.03; patients w/metastatic disease: 60% versus 56% (P = 0.46); 0.03: 2-year survival estimates of 78% and 55%, respectively, and 3-year estimates of 60% and 36% [93]. In a prespecified analysis by life expectancy in another of these trials, the hazard ratios with nadroparin versus placebo were 0.61 (95% CI 0.42–0.89) for patients expected to live for 6 months or longer and 0.82 (95% CI 0.51–1.29) for those expected to live for <6 months [95]. In a retrospective analysis of data from the CLOT study, patients without metastases had a significantly lower 1-year mortality rate with dalteparin than with oral anticoagulation (Kaplan–Meier estimates: 20% and 34.7%, respectively; P = 0.03), and this advantage persisted after adjustment for differences in baseline risk factors [97]. In contrast, among patients with known metastatic disease, the estimates for 1-year mortality with dalteparin did not differ significantly from those with oral anticoagulation (72% and 69%, respectively; P = 0.46). Again, these studies cannot evaluate a direct antitumor effect of anticoagulation, particularly LMWHs, although preclinical studies have suggested such an effect [97].

A recent meta-analysis also showed that anticoagulants, particularly LMWH, significantly improved overall survival in cancer patients without VTE but also increased the risk of bleeding complications. Fatal bleeding events were extremely rare, however, and LMWHs appeared to have a more favorable bleeding profile than VKAs did [98]. Nonetheless, a recent Cochrane review showed that with respect to long-term treatment of VTE in patients with cancer, LMWH treatment reduced VTE as compared with VKA treatment but did not reduce mortality [76]. This finding may be due to the study's lack of sufficient statistical power to detect a reduction in all-cause mortality, even though the results might indicate a trend in that direction. Additional well-designed randomized clinical trials are necessary to address the impact of LMWH on survival in cancer patients.

The mechanism by which LMWH might provide a survival benefit, beyond the prevention of VTE, is not known. The observation that LMWH exhibited a clearer advantage in the second survival study [94] than in the first [93] might be explained by the fact that small-cell lung cancer is known to express a thrombin-generating pathway with local fibrin formation [94]. Of note, a recent in vitro study suggests that LMWHs may exert their antitumor effects through inhibition of cell growth and proliferation [99]. This study showed that that dalteparin inhibited pulmonary adenocarcinoma cell viability in a dose- and time-dependent manner, caused G1 phase cell cycle arrest, and induced apoptosis. Another recent in vitro study supports the role of LMWHs in inhibiting the proangiogenic effect exerted by tumor cells [100]. This study demonstrated that both dalteparin and enoxaparin inhibited the tumor-promoted angiogenic potential of human microvascular endothelial cells to a significantly greater degree.
than UFH did. These results are consistent with those of another study, which showed that the 6-kDa LMWH fraction inhibited the proliferation of human umbilical vein endothelial cells significantly more than either UFH or 3-kDa LMWH did. No inhibition of proliferation was observed with heparin tetrasaccharide, octasaccharide, or pentasaccharide (fondaparinux) [101]. Because the 6-kDa fraction, which exerted maximum endothelial inhibitory effects, is similar to LMWHs currently in clinical use, which range from 4 to 5.5 kDa, its antiproliferative effect on endothelial cells may be relevant to the biology of malignancy and may explain the therapeutic effect of LMWHs on survival in cancer patients. Further clinical research is needed to clarify the possible survival benefits of LMWH in patients with various types of tumors and to examine whether extending LMWH therapy beyond the duration of chemotherapy might offer incremental benefit.

**summary**

VTE is the second most common cause of death in patients with cancer [1, 90]. Risk factors for cancer-associated VTE include chemotherapy, the use of antiangiogenic agents or ESAs, surgery, and the presence of CVCs [14].

Anticoagulant therapy is efficacious for prophylaxis and treatment of VTE in patients with cancer. LMWHs offer several advantages over UFH and warfarin, including more consistent anticoagulant effects, no requirement for frequent laboratory monitoring, and few drug–drug and drug–nutrient interactions. LMWHs thus represent the preferred therapeutic option for VTE prophylaxis and treatment in most cases. The use of LMWHs may also be associated with improved survival in oncology patients, although further study of patients with various types and stages of tumors will be required to settle this issue.

Despite the significant impact of VTE and the demonstrated effectiveness of anticoagulant therapies, many oncology patients still are not receiving VTE prophylaxis and treatment as recommended by clinical practice guidelines [14, 16]. Improved adherence to such guidelines could substantially decrease morbidity, reduce resource use, enhance quality of life, and, most important, increase survival in this patient population.

**conflict of interest**

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**references**


