The NCCN Clinical Practice Guidelines on Venous Thromboembolic Disease: Strategies for Improving VTE Prophylaxis in Hospitalized Cancer Patients

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Key Words. Venous thromboembolism • Cancer • Anticoagulation • Prophylaxis • Clinical practice guideline

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the importance of thromboprophylaxis in hospitalized cancer patients.
2. Identify risk factors for cancer-associated thrombosis.
3. Identify strategies to improve compliance with prophylaxis recommended by NCCN guidelines.

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ABSTRACT

The risk for venous thromboembolism (VTE) is high in hospitalized cancer patients, and is associated with an elevated risk for recurrent thrombosis, bleeding complications, and use of health care resources. Thromboprophylaxis is the second leading cause of death in hospitalized cancer patients. Thromboprophylaxis with unfractionated heparin or low-molecular-weight heparins has been clinically proven to reduce the risk for VTE and improve outcomes. However, VTE prophylaxis continues to be underprescribed in cancer patients. Recognizing the clinical burden of VTE in cancer patients, the National Comprehensive Cancer Network (NCCN) recently released guidelines for VTE prevention and management. These NCCN guidelines recommend evidence-based prophylactic anticoagulant therapy for all patients admitted to hospital with a diagnosis of cancer who do not have contraindications to anticoagulant use. However, there continue to be barriers to the implementation of clinical practice guidelines and appropriate use of VTE prophylaxis. Multifaceted active educational and electronic interventions are necessary to raise awareness and reduce the burden of cancer-associated thrombosis and its attendant consequences.

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INTRODUCTION

Studies have long reported the association between cancer and venous thromboembolism (VTE), which comprises both deep-vein thrombosis (DVT) and pulmonary embolism (PE). Several mechanisms have been proposed to explain this association, including the release of procoagulant factors by the tumor, reduced fibrinolytic activity, and extrinsic venous compression by the tumor. The prothrombotic state in cancer is further enhanced by antineoplastic therapy including surgical procedures, chemotherapy, central venous catheters, and supportive care agents [1]. There is an estimated fivefold higher annual incidence of VTE in cancer patients, with about 1 in 1,000 in the general population and 1 in 200 in cancer patients [2]. In a recent retrospective study involving more than 66,000 hospitalized neutropenic adults with cancer, 5.4% of patients developed VTE over the 8 years of the study [3]. VTE is the second leading cause of in-hospital death, after cancer, in cancer patients [4].

Robust evidence from multiple, large, randomized studies shows that prophylactic anticoagulation significantly reduces the incidence of thrombotic complications [5–7]. Based on these data, consensus guidelines from multiple specialty organizations provide clear recommendations for the prevention and treatment of VTE, and highlight the need for prophylaxis in cancer patients [8–10]. Despite this, VTE prophylaxis remains underused in cancer patients [11]. In fact, admission for cancer has even been associated with a lower likelihood of VTE prophylaxis [12].

The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 20 of the world’s leading cancer centers with the mission to improve the care of cancer patients. It publishes one of the most widely used clinical guidelines in oncology practice, which includes guidelines on areas of supportive care, such as prevention of thromboembolic disease [13]. These NCCN guidelines recommend “prophylactic anticoagulation therapy for all inpatients with a diagnosis of active cancer (or for whom clinical suspicion of cancer exists) who do not have a contraindication to such therapy” [13]. Inclusion of recommendations in the NCCN core guidelines regarding the management of VTE disease is expected to increase the use of appropriate VTE prophylaxis and treatment in hospitalized patients with cancer. This will ultimately improve the standard of patient care and thus help prevent avoidable VTE and its related life-threatening complications.

RISK FOR VTE IN CANCER PATIENTS

The presence of cancer is a well-recognized independent risk factor for VTE [14, 15], and almost one fifth of all new VTE events are associated with active cancer [16]. Epidemiological studies have shown that the risk for VTE is significantly higher in patients with cancer [14, 17, 18]. In a population-based case-control study, the overall risk for VTE was sevenfold higher in patients with cancer than in those without malignancy (odds ratio [OR], 6.7; 95% confidence interval [CI], 5.2–8.6) [17]. Among hospitalized patients, those with cancer had twice the incidence of VTE as those without [18].

Patients with cancer who develop VTE also have a higher risk for recurrent thrombotic complications than VTE patients without malignancy [19–23]. It has been reported that the risk for recurrent thrombotic events is twice as high in patients with malignancy as in those without cancer, and four times higher if patients are concurrently receiving chemotherapy [20]. In a retrospective analysis of Medicare claims data over a 3-year period, patients with DVT and/or PE and cancer were found to have a threefold higher risk for recurrent VTE than patients who had an initial DVT and/or PE in the absence of malignancy [19]. The probability of readmission for recurrent VTE within 183 days was 0.22 for cancer patients compared with 0.065 for those without malignancy (p = .001) [19]. Similarly, Pandoni et al. [21] have reported that the risk for recurrent VTE is four times higher in patients with cancer than in those without the disease.

The risk for VTE is also influenced by the type of cancer. Malignant brain tumors, hematologic malignancies, and adenocarcinomas of the pancreas, uterus, ovary, stomach, lung, and kidney are considered to carry the highest risk for VTE [3, 17–19, 24–26]. It should be noted, however, that the frequency at which VTE occurs for a certain type of cancer might reflect both the thrombotic risk and the proportion of that cancer in the population. For example, Khorana et al. [3] reported that more than one third of all VTE events in over 66,000 patients occurred in patients with non-Hodgkin’s lymphoma or leukemia. These are both cancers that are not commonly perceived as high risk regarding VTE but that represent one fifth of the study population each [3]. Therefore, VTE prophylaxis should focus not only on cancers associated with a high risk for VTE but also on the common cancers seen in hospitalized patients. Thrombotic risk may also be influenced by the extent of the malignancy, and data suggest that advanced metastatic cancer is associated with a higher risk for VTE [3, 17, 24, 27, 28]. Similarly, the risk for VTE recurrence appears to be higher in patients with more extensive disease: a nearly fivefold higher recurrence rate has been reported in patients with advanced disease compared with a two- to threefold higher risk in those with more localized tumors [21].

Treatments for cancer may also increase the risk for VTE. Patients receiving chemotherapy or hormonal ther-
apy or undergoing surgery for cancer have at least twice the risk for VTE compared with patients who never underwent these treatments [14, 24, 29–31]. For example, a U.S. population-based survey of risk factors for VTE reported that the incidence of VTE in patients with cancer was 4.1 times higher than in patients with no malignancy, and this risk was 6.5-fold higher in cancer patients receiving chemotherapy [14]. Similarly, surgical intervention places cancer patients at a twofold higher risk for postoperative VTE compared with noncancer patients undergoing the same procedure [28].

The thrombotic risk in cancer patients is likely to be further increased because of concomitant noncancer-specific VTE risk factors such as advanced age, debility, prolonged immobilization, hospitalization, surgery, and the presence of comorbid conditions such as respiratory failure or congestive heart failure [14, 15, 18, 29].

**Mortality in Patients with Cancer and VTE**

Thromboembolism has a significant adverse impact on survival in patients with cancer. Cancer patients who develop DVT or PE have a shorter life expectancy than either cancer patients without VTE or noncancer patients with VTE [3, 19, 27, 32, 33]. For example, in patients with VTE the risk for death after an acute VTE event was eightfold higher in cancer patients than in patients without malignant disease (OR, 8.1; 95% CI, 3.6–18.1) [33]. Conversely, among hospitalized cancer patients, a diagnosis of VTE has been associated with a twofold higher risk for mortality (OR, 2.01; 95% CI, 1.83–2.22; p < .0001) [3].

Of particular concern is the greater in-hospital mortality associated with VTE in patients with nonmetastatic disease and a favorable prognosis. Older studies have reported that as many as one in seven hospitalized cancer patients die from a PE rather than their cancer, and that up to 60% of all cancer patients who died from a PE had localized or limited metastatic cancer that would otherwise have allowed for reasonably long survival in the absence of PE [34]. A more contemporary study of a large population of hospitalized neutropenic cancer patients confirmed the higher in-hospital mortality associated with VTE even in nonmetastatic disease (OR, 1.62; 95% CI, 1.37–1.91; p < .0001) [3].

VTE is also a leading cause of death in ambulatory cancer patients receiving chemotherapy, with deaths from thromboembolism accounting for nearly 10% of all deaths in such patients [35]. This represents a 47-fold higher death rate from VTE than seen in the general population (95% CI, 6–89; p = .03).

**Benefits of Prophylactic Anticoagulation: The Evidence in Cancer Patients**

**Prevention of VTE**

Thromboprophylaxis with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) can improve outcomes and reduce mortality rates in both medical and surgical patients, including cancer patients.

**Surgical Cancer Patients**

The benefit of prophylactic anticoagulation in surgical oncology patients is long established [8]. For example, the Enoxaparin and Cancer (ENOXACAN) trial in patients undergoing curative abdominal or pelvic surgery for cancer showed that, given 2 hours preoperatively and for 10 ± 2 days postsurgery, the LMWH enoxaparin at 40 mg once daily is as effective and well tolerated as UFH at 5,000 IU three times daily in reducing the incidence of thromboembolic complications postsurgery [5]. VTE incidences were 14.7% with LMWH and 18.2% with UFH prophylaxis (95% CI for the difference, −9.2 to 2.3). There was no significant difference in the incidence of bleeding between the two regimens; 18.7% with LMWH and 17.1% with UFH prophylaxis. A meta-analysis of clinical trials involving LMWH in general surgery, which included a cancer-related surgery subgroup analysis, subsequently confirmed that the efficacy and safety profiles of LMWH and UFH are similar for the prevention of VTE in patients with cancer [36].

The majority of prophylactic UFH or LMWH regimens are 7–10 days in duration; however, patients at high risk for VTE, such as those undergoing cancer surgery, may benefit from an extended prophylactic regimen. Extended 40-mg once-daily enoxaparin prophylaxis for 4 weeks in patients undergoing major abdominal surgery for cancer led to a significantly lower incidence of VTE compared with the standard 1-week prophylactic regimen (4.8% and 12.0%, respectively; p = .02) [37]. There was no significant difference in the incidence of bleeding (5.1% and 3.6%, respectively; p = .51). Therefore, the NCCN guidelines recommend continuation of prophylaxis after hospital discharge in high-risk cancer patients such as those undergoing cancer surgery [13].

**Medical Cancer Patients**

There are far fewer data on the safety and efficacy of thromboprophylaxis in hospitalized medical cancer patients. However, clinical trials in hospitalized medical patients, which included cancer patients, have demonstrated that LMWH prophylaxis leads to a lower VTE incidence compared with placebo, without increasing major bleeding [6, 7]. A meta-analysis of randomized trials comparing
Antitumor Effects of LMWHs

In addition to preventing thromboembolic complications, studies have suggested that anticoagulation with LMWHs may also offer additional benefits through direct antitumor properties [39]. The mechanisms by which LMWHs exert these direct effects have yet to be elucidated, but their antitumor actions appear to include inhibition of angiogenesis, inhibition of the release of coagulation proteases, immunomodulatory actions, and apoptosis [40].

Randomized controlled clinical trials conducted in cancer patients without VTE have reported higher survival rates in patients receiving prophylactic doses of LMWH compared with no treatment or placebo [41–43]. Patients with small cell lung cancer treated with combination chemotherapy (CT) had a lower risk for death when receiving concomitant prophylactic LMWH during the 18 weeks of CT (relative risk [RR], 0.56; 95% CI, 0.30–0.86; p = .012) [41]. Similarly, in a study of patients with metastasized or locally advanced solid tumors, a 6-week course of prophylactic LMWH led to a significantly longer survival time compared with placebo (OR, 0.64; 95% CI, 0.45–0.90) in patients with a life expectancy ≥6 months [43]. A trend toward longer survival was also observed in patients with a life expectancy <6 months receiving LMWH (OR, 0.88; 95% CI, 0.62–1.25) [43]. Because the benefit in survival time has not been consistently observed in patients with advanced metastatic disease receiving prophylactic LMWH for 1 year [42], the antineoplastic effects of LMWHs require further investigation. However, a recent meta-analysis of randomized trials in cancer patients concluded that the addition of prophylactic LMWH to conventional cancer treatment resulted in a longer overall survival time than with placebo or no anticoagulant intervention (RR, 0.87; 95% CI, 0.77–0.99; p = .04) [44]. The use of LMWH conferred a survival benefit even when considering only patients with advanced cancer (RR, 0.89; 95% CI, 0.80–0.99; p = .03). Our group recently conducted a comprehensive systematic review and meta-analysis of all anticoagulant studies in cancer [45]. Across all 11 identified studies, anticoagulation resulted in a significantly lower overall risk for mortality (RR, 0.905; 95% CI, 0.847–0.967; p = .003).

Table 1. National Comprehensive Cancer Network (NCCN) recommendations for inpatient thromboprophylactic anticoagulation therapy

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Mode of action</th>
<th>Prophylactic dose</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Antithrombin potentiator (thrombin and factor Xa inhibition)</td>
<td>5,000 IU s.c. three times daily</td>
<td>Duration of hospital stay</td>
</tr>
<tr>
<td>Dalteparin (LMWH)</td>
<td>Antithrombin potentiator (factor Xa inhibition and some thrombin inhibition)</td>
<td>5,000 IU s.c. daily</td>
<td>Duration of hospital stay</td>
</tr>
<tr>
<td>Enoxaparin (LMWH)</td>
<td>Antithrombin potentiator (factor Xa inhibition and some thrombin inhibition)</td>
<td>40 mg s.c. daily (30 mg s.c. daily in patients with reduced renal function)</td>
<td>Duration of hospital stay</td>
</tr>
<tr>
<td>Tinzaparin (LMWH)</td>
<td>Antithrombin potentiator (factor Xa inhibition and some thrombin inhibition)</td>
<td>4,500 IU s.c. daily (or 75 IU/kg s.c. daily)</td>
<td>Duration of hospital stay</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Specific anti–factor Xa inhibitor</td>
<td>2.5 mg s.c. daily</td>
<td>Duration of hospital stay</td>
</tr>
</tbody>
</table>

LMWHs and fondaparinux must be used with caution in patients with renal insufficiency and failure; dose adjustments may be required in patients with creatinine clearance <30 ml/minute.

These guidelines are a work in progress that will be refined as new significant data become available. The NCCN guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by the NCCN. All rights reserved. These guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN.

Abbreviation: LMWH, low-molecular-weight heparin.

The relative risk for mortality was 0.877 (95% CI, 0.789–0.975; \( p = 0.015 \)) with LMWH, compared with 0.942 (95% CI, 0.854–1.040; \( p = 0.239 \)) with warfarin, resulting in an 8% absolute risk difference (ARD) for LMWH and 3% for warfarin. Major bleeding episodes occurred less frequently in LMWH patients (ARD, 1%) than in warfarin patients (ARD, 11.5%) (\( p < 0.0001 \)).

A retrospective analysis based on nearly 2.5 million patient hospital discharges, obtained from a large U.S. inpatient database, has shown that the mortality rate in cancer patients who received thromboprophylaxis with UFH or LMWH was significantly lower than for cancer patients who did not receive prophylaxis (risk-adjusted mortality rate, 7.4% versus 8.6%, respectively; \( p < .001 \)) [46]. Therefore, thromboprophylaxis in cancer patients might also improve their survival outcomes, possibly by preventing VTE and by additional antitumor effects. However, this hypothesis requires further testing in randomized controlled trials. Moreover, the specific properties and mode of action of the various thromboprophylactic agents lead to different mechanisms and extent of affecting tumors [47]. Knowledge of such mechanisms could result in better, targeted thromboprophylaxis.

**Recommended Thromboprophylactic Regimens in Cancer Patients**

The NCCN guidelines, Seventh American College of Chest Physicians (ACCP) guidelines [8], and the latest International Union of Angioplasty (IUA) guidelines [9] all categorize hospitalized cancer patients as a group at high or highest risk for VTE who should be considered for pharmacological thromboprophylaxis, provided no contraindications to anticoagulant therapy exist (Fig. 1).

For cancer patients without contraindications to anticoagulant therapy, several regimens have been shown to provide effective and well-tolerated prophylaxis against VTE in patients with cancer and are recommended in the NCCN, as well as the ACCP and IUA, guidelines. These include the LMWHs dalteparin, enoxaparin, and tinzaparin, the pentasaccharide fondaparinux, and UFH (Table 1). Enoxaparin and dalteparin are the only LMWHs that have been approved by the U.S. Food and Drug Administration (FDA) for VTE prophylaxis. Tinzaparin is not currently FDA-approved for VTE prophylaxis. The pentasaccharide fondaparinux is not currently approved for VTE prophylaxis in medically ill patients in the U.S., but has received approval in the European Union.

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**Figure 1.** Algorithm for initial venous thromboembolism prophylaxis. These guidelines are a work in progress that will be refined as often as new significant data become available. The National Comprehensive Cancer Network (NCCN) guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by the NCCN. All rights reserved. These guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. From National Comprehensive Cancer Network. Venous Thromboembolic Disease Clinical Practice Guidelines in Oncology (V.1.2007). Available at http://www.nccn.org/professionals/physician_gls/PDF/vte.pdf, with permission.
Cancer patients with contraindications to anticoagulants should receive continuous mechanical prophylaxis with sequential compression devices (SCDs) or graduated compression stockings. Relative contraindications to either prophylactic or therapeutic anticoagulant therapy are also listed in the NCCN guidelines [13].

Although there have been few studies evaluating the benefits of combined mechanical and pharmacological prophylaxis in medical populations, the NCCN guidelines recommend that mechanical prophylaxis with SCDs be given to all hospitalized patients with cancer, in combination with pharmacological prophylaxis if there are no contraindications [13].

**Table 2. Relative contraindications to thromboprophylactic or therapeutic anticoagulation therapy from the National Comprehensive Cancer Network (NCCN)**

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding (major):</td>
<td>&gt;2 units transfused in 24 hours</td>
</tr>
<tr>
<td>Chronic, clinically significant measurable bleeding</td>
<td>&gt;48 hours</td>
</tr>
<tr>
<td>Thrombocytopenia (platelets &lt; 50,000/µl)</td>
<td></td>
</tr>
<tr>
<td>Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)</td>
<td></td>
</tr>
<tr>
<td>Recent major operation at high risk for bleeding</td>
<td></td>
</tr>
<tr>
<td>Underlying coagulopathy</td>
<td></td>
</tr>
<tr>
<td>Clotting factor abnormalities</td>
<td></td>
</tr>
<tr>
<td>Elevated prothrombin time or activated partial thromboplastin time (excluding lupus inhibitors)</td>
<td></td>
</tr>
<tr>
<td>Spinal anesthesia/lumbar puncture</td>
<td></td>
</tr>
<tr>
<td>High risk for falls</td>
<td></td>
</tr>
</tbody>
</table>

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**UNDERUSE OF PROPHYLAXIS IN HOSPITALIZED CANCER PATIENTS**

Despite recognition of the high risk for VTE faced by cancer patients, and strong expert recommendations that cancer patients should receive thromboprophylaxis, there is evidence that prophylaxis is underused in hospitalized medical patients. A 4-year retrospective study of thromboprophylaxis practices in medically ill patients across the U.S. revealed low rates of thromboprophylaxis for patient groups who are at risk for VTE, including cancer patients [46]. Although the use of prophylaxis in cancer patients improved slightly between 2001 and 2004, from 18% to 25%, it still remained at an unacceptably low percentage [46].

The Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey, which assessed opinions and prescribing practices relating to VTE in cancer patients, reported that, while >50% of surgeons reported routinely using thromboprophylaxis, medical oncologists reported doing so in <5% of their patients [11]. Similarly, a recent Canadian multicenter hospital audit of thromboprophylaxis use in medical inpatients found that patients admitted for cancer were significantly less likely to receive any form of VTE prophylaxis than other medical patients (OR, 0.40; 95% CI, 0.24–0.68; \( p = 0.0007 \)) [12].

**REASONS FOR UNDERUSE OF PROPHYLAXIS**

A perceived barrier to VTE prophylaxis may be the procoagulant effects resulting from the malignant state that may render VTE treatment less effective and increase bleeding complications during anticoagulant therapy [8, 21]. In the Registro Informatizado de Pacientes con Enfermedad Tromboembólica (RIETE) registry, the incidence of fatal PE was 2.6%, whereas fatal bleeding occurred in 1.0% of cancer patients with acute symptomatic VTE [48]. Although these patients were receiving therapeutic doses of anticoagulants, the incidence of fatal PE remained higher than that of fatal bleeding. However, in trials of thromboprophylaxis in medical patients involving LMWH, the rate of major bleeding complications was not higher in cancer patients receiving prophylaxis [5–7, 49]. Indeed, LMWH has been shown to be as effective as UFH in preventing
VTE in hospitalized medical patients with significantly fewer bleeding complications [38].

Underestimation of the risk for VTE could also be partially responsible for poor use of thromboprophylaxis. The FRONTLINE survey of prophylaxis practices in cancer treatment reported that, contrary to clinical evidence, most medically treated cancer inpatients were thought to have a low risk for VTE (<10%) [11].

Another possibility is that physicians are unaware of currently recommended VTE management strategies. A U.S. survey of physicians’ knowledge and practices in thrombosis management reported a number of gaps in physicians’ knowledge, including the current standards for the treatment of symptomatic calf-vein thrombosis [50].

Furthermore, a general survey of barriers to uptake of clinical practice guidelines identified a number of physician-related factors as possible barriers to adherence, such as lack of familiarity, lack of agreement with the guidelines, lack of confidence in implementing the guidelines, belief that implementing the guidelines is ineffective in improving outcomes, and overcoming resistance to changing established practice patterns [51]. However, even with the appropriate awareness and motivation levels to implement clinical guidelines, external barriers may prevent or limit effective adoption of expert advice. These include the need to acquire approval and funding for new drugs or equipment in order to implement recommendations, the need to educate and persuade patients to accept guideline recommendations, and the clarity and ease of use of the guidelines themselves [51].

**IMPROVING THE IMPLEMENTATION OF GUIDELINES**

Closing the “quality gap” between the availability of evidence-based clinical guidelines and their implementation is a key initiative in increasing thromboprophylaxis rates in cancer patients and improving outcomes. Continuing education of health care provider teams and patients, decision support tools, regular clinical audit-and-feedback pro-

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### Table 3. Strategies to improve implementation of venous thromboembolism (VTE) prophylaxis guidelines in cancer patients

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Example(s) in VTE management</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational initiatives (health care provider)</td>
<td>Workshops and peer-led presentations</td>
<td>Generally effective in increasing knowledge but ineffective as a sole intervention to change prescribing practices. Active interventions (e.g., workshops) usually more effective than passive ones (e.g., mailings)</td>
</tr>
<tr>
<td></td>
<td>Printed material from conferences or expert bodies/societies</td>
<td></td>
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<tr>
<td></td>
<td>Educational outreach visits</td>
<td></td>
</tr>
<tr>
<td>Decision support tools</td>
<td>Risk assessment models and prophylaxis reminders in admission charts</td>
<td>Decision support tools have been shown to have efficacy in improving prophylaxis and improving outcomes. Reminders systems work best if well integrated with the clinical workflow (e.g., electronic alerts as part of computerized admission order entry systems)</td>
</tr>
<tr>
<td></td>
<td>Computer-based reminders/alerts for physicians accompanied by recommendations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Computer-aided decision support programs</td>
<td></td>
</tr>
<tr>
<td>Audit and feedback process</td>
<td>Individual or team-based clinical feedback sessions</td>
<td>Variable efficacy (small to modest improvements) as a stand-alone initiative. Works well as part of an integrated program. Good results reported when feedback led by clinical authority figure</td>
</tr>
<tr>
<td></td>
<td>Quality indicators and reports</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benchmarking against outcomes from highest performing provider</td>
<td></td>
</tr>
<tr>
<td>Organizational changes</td>
<td>Multidisciplinary team approach to case management</td>
<td>Not studied as individual interventions, but can form a valuable part of a multifaceted approach to improving VTE management</td>
</tr>
<tr>
<td></td>
<td>Integrated care pathways</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Changing from paper to computer-held patient records</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased levels of nursing care</td>
<td></td>
</tr>
<tr>
<td>Regulations and policy changes (including financial incentives)</td>
<td>Financial bonus achieved by attaining target levels of compliance with guidelines/outcomes improvements</td>
<td>Some efficacy but can lead to conflict of interest within teams</td>
</tr>
<tr>
<td></td>
<td>Alternative reimbursement schemes (e.g., change from fee-for-service to capitated reimbursement)</td>
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cesses, organizational changes, regulation and policy changes, and achievement incentives have been trialed as quality improvement (QI) strategies in clinical practice [52] (Table 3). A review of the effectiveness of individual QI methods concluded that no single intervention was outstanding in its effectiveness, rather that the most effective strategies integrated several QI approaches. Equally, active interventions, such as audit and feedback systems, were found to be more effective than passive ones, such as educational mailings [53].

Implementation of educational and QI strategies has been shown to improve thromboprophylaxis rates [54–57] and reduce the prevalence of VTE [56, 58]. Prescribing tools have been proven to be valuable in increasing prophylaxis uptake. The introduction of an electronic prescribing alert successfully increased prophylaxis rates and reduced the incidence of VTE in hospitalized patients at risk for thrombosis [56]. Alternatively, VTE risk assessment models and optimal VTE prevention regimens can be included in hospital admission forms [55]. However, an integrated multiple intervention approach appears to be the most effective [55, 57, 58]. Cohn et al. [57] recently reported striking success using an integrated approach involving regular provider education (active, monthly, staff orientation by the chief resident on VTE risk and management, posters to reinforce messages, and in-hospital education of nurses by the nurse educator), a decision support tool (a pocket card summarizing VTE risk factors and recommended prophylactic options), and most importantly, a monthly audit on the type and appropriateness of prophylaxis prescribed carried out by the Chief of Internal Medicine [57]. This program resulted in a significant increase in the proportion of patients who received appropriate prophylaxis in accordance with the ACCP guidelines from 42.9% at the start of the study to 68.1% after 12 months, and 85.0% after 18 months (p < .01 at both time points) [57]. Similar improvements have been reported with a pharmacy education program presented to nurses, pharmacists, and physicians of a community teaching hospital, and involving multiple educational initiatives combined with quality assurance presentations on VTE prophylaxis [54].

One of the key strengths of the NCCN guidelines is that the recommendations have been presented in a concise and graphic format, supported by succinct explanatory notes [13]. The algorithms in the VTE management guidelines can easily be incorporated into decision support/prescribing tools to facilitate and encourage the use of appropriate VTE prophylaxis in all hospitalized cancer patients.

Recognizing the clinical and economic importance of improved VTE management, quality improvement organizations such as the Agency for Healthcare Research and Quality, the National Quality Forum, the Joint Commission, and the Surgical Care Improvement Project have launched multifaceted programs to improve VTE prophylaxis. To ensure widespread dissemination and appropriate use of the NCCN guidelines for the management of VTE and consequently to reduce the burden of VTE, oncology teams need to implement an integrated approach involving many of the highlighted QI interventions.

**CONCLUSIONS**

Cancer patients are at high risk for developing thrombosis and recurrent VTE complications. Effective thromboprophylaxis reduces the risk for VTE and improves outcomes. However, VTE prophylaxis remains significantly underused in cancer patients. The latest NCCN guidelines recommend evidence-based prophylactic anticoagulant therapy for all inpatients with a diagnosis of cancer (or in whom cancer is suspected) who do not have contraindications to anticoagulant use. Clinical experience indicates that simple dissemination of expert guidelines is insufficient to ensure adoption. Multifaceted strategies to raise awareness, and ensure implementation, of these guidelines are required to enhance awareness on the risk for VTE encountered by cancer patients, and promote adequate VTE prophylaxis for hospitalized patients with cancer.

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