ABSTRACT

Patients with cancer are at high risk of developing arterial and venous thromboembolism (VTE). They constitute 15% to 20% of the patients diagnosed with VTE. Depending on the type of tumor, cancer therapy, and presence of other risk factors, 1% to 25% of patients with cancer will develop thrombosis. The decision to start patients with cancer on primary thromboprophylaxis depends on patient preference, balancing risk of bleeding versus risk of thrombosis, cost, and adequate organ function. Currently, guidelines recommend against the use of routine primary thromboprophylaxis in unselected ambulatory patients with cancer. Validated risk assessment models can accurately identify patients at highest risk for cancer-associated thrombosis (CAT). This review summarizes the recently updated NCCN Guidelines for CAT primary prophylaxis, with a primarily focus on VTE prevention. Two main clinical questions that providers commonly encounter will also be addressed: which patients with cancer should receive primary thromboprophylaxis (both surgical and medical oncology patients) and how to safely choose between different anticoagulation agents.

In 1823, Jean-Baptiste Bouillaud published the first report of an association between thrombosis and cancer. In 1865, Trousseau identified the association between gastric cancer and venous thrombosis, and the combination of the 2 conditions is still referred to as Trousseau syndrome. Patients with cancer constitute 15% to 20% of the patients diagnosed with venous thromboembolism (VTE). Depending on the type of tumor, cancer therapy, and presence of other risk factors, 1% to 25% of patients with cancer will develop thrombosis (Table 1). Cancer-associated thrombosis (CAT), including both venous and arterial events, is the second leading cause of death in patients with cancer. This review summarizes the recently updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CAT primary prophylaxis guidelines, with a primarily focus on VTE prevention. We also address 2 main clinical questions that providers usually encounter: (1) which patient with cancer should receive primary thromboprophylaxis? and (2) how do clinicians choose safely between different anticoagulation agents?

Identifying Patients At Risk for CAT

Initial Period After Cancer Diagnosis

Patients with cancer have an increased risk of CAT during the first few months after diagnosis, and the risk then decreases as time progresses. This might be explained by the fact that most of the therapeutic interventions, such as chemotherapy and central venous catheter placement, occur during this period. In a large population-based study, the odds ratio (OR) for developing VTE in the first 3 months after cancer diagnosis was 53.5 (95% CI, 8.6–334.3), declining to 14.3 (95% CI, 5.8–35.2) and 3.6 (95% CI, 2.0–6.5) in the 3 months to 1 year and 1 to 3 year intervals, respectively.

Cancer Stage and Type

Patients with advanced-stage disease and distant metastasis have a greatly increased CAT risk. Lymphoma and multiple myeloma carry the highest CAT risk among hematologic malignancies, whereas brain and gastrointestinal cancers carry the highest CAT risk among solid malignancies. Risk of thrombosis also varies by cancer histologic subtype. In patients with non–small cell lung

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Abbreviation: CAT, cancer-associated thrombosis.

cancer, incidence of VTE is increased 3-fold in those with adenocarcinoma compared with those with squamous cell carcinoma (Table 1).10

Chemotherapy-Related Risk Factors
Patients receiving anticancer agents are at a higher risk of CAT (Table 1).11-12 Anticancer agents may induce a pro-thrombotic state through several mechanisms, including vascular endothelial damage, reduced levels of endogenous anticoagulants, induction of tissue factor procoagulant activity, and activation of platelets.13,14

Patient-Related Risk Factors
Inherited thrombophilia could also have an increased risk of CAT. Carriers of the factor V Leiden and prothrombin 20210A mutation who had cancer have a 12-fold increased risk compared with individuals without cancer and factor V Leiden or prothrombin 20210A mutation (adjusted OR, 12.1; 95% CI, 1.6-88.1).8 Other risk factors include prior history of thrombosis, obesity, and advanced age (Table 1).

VTE Risk Assessment in Ambulatory Patients With Cancer
CAT risk assessment models (RAMs) help identify a population of patients with cancer at highest risk for thrombosis. The Khorana risk stratification score was originally introduced in 2008 and is currently endorsed by the latest NCCN Guidelines updates to select ambulatory patients with cancer for thromboprophylaxis. This score contains 5 predictive variables; primary tumor site, platelet count of ≥350 × 109/L, hemoglobin concentration of ≤100 g/L or use of erythropoiesis-stimulating agents, leukocyte count of ≥11 × 109/L, and a body mass index (BMI) of ≥35 kg/m².15 The rate of symptomatic VTE in the low-, intermediate-, and high-risk categories was 0.3%, 2%, and 6.7%, respectively, over a median follow-up of 2.5 months.15

CAT Prevention in Surgical Oncology Patients
Patients with cancer undergoing abdominal and pelvic surgeries are at an increased risk of CAT. The risk remains high for several weeks after major surgeries and can reach up to 29% without using primary thromboprophylaxis.16 Enoxaparin postoperative prophylaxis for 4 weeks is safe and significantly reduces the risk of thrombosis.17-18 A double-blind, multicenter trial randomized 322 patients undergoing open surgeries for abdominal or pelvic cancer into either 1 week or 4 weeks of enoxaparin postoperative prophylaxis, and found that enoxaparin prophylaxis for 4 weeks significantly lowered the incidence of postoperative thrombosis (4.8% vs 12% for 4 weeks and 1 week of prophylaxis, respectively; P = .02). This difference persisted at 3 months (5.5% vs 13.8%, respectively; P = .01).17 The benefit of extended enoxaparin prophylaxis in decreasing VTE after abdominal and pelvic surgery was further confirmed by a meta-analysis of 4 randomized controlled trials.18 However, it is worth noting that the majority of VTEs after abdominal and pelvic surgery were asymptomatic and confined to the lower extremities. These VTE events had low potential to embolize, as confirmed by the fact that the postoperative pulmonary embolism rates were similar for the 2 groups.18

Failure of compliance with low-molecular-weight heparin (LMWH) might increase the risk of postoperative thrombosis. Although the rate of adherence to outpatient postoperative thromboprophylaxis has not been elucidated in patients with cancer, data from the pediatrics literature identified an adherence rate of approximately 60%.19 Common reason for the low adherence rate to LMWH include injection site reaction and pain. Direct oral anticoagulant agents (DOACs) might be a more convenient alternative for postoperative thromboprophylaxis. In a multicenter prospective trial, 400 postoperative patients with gynecologic cancer were randomized to prophylactic oral apixaban versus subcutaneous enoxaparin.20 No differences were identified between groups for rates bleeding or thrombotic events. However, participant satisfaction with ease of taking the medication was significantly greater in the apixaban group.20
NCCN Guidelines Recommendations

- Extended CAT prophylaxis is recommended for up to 4 weeks after major abdominal and pelvic surgyes.
- CAT prophylaxis options include enoxaparin, 40 mg subcutaneously daily for 28 days; dalteparin, 5,000 units subcutaneously daily for 28 days; and apixaban, 2.5 mg orally twice per day for 28 days.

CAT Prevention in Ambulatory Solid Oncology Patients

CAT among solid oncology patients receiving chemotherapy could be associated with poor clinical outcomes. There might be an increased risk of disease progression with chemotherapy interruption, and increased risk for serious bleeding due to the need for anticoagulation.

PROTECHT, a randomized double-blind multicenter trial, evaluated the efficacy and safety of nadroparin for CAT prevention in 1,150 ambulatory patients receiving chemotherapy for metastatic or locally advanced solid malignancy. Nadroparin significantly reduced the incidence of CAT (2% and 3.9% in the nadroparin and placebo groups, respectively) without a significant effect on major bleeding (0.7% and 0% in the nadroparin and placebo groups, respectively). However, it is worth noting that the PROTECHT study was not powered to detect differences in major bleeding.

SAVO-ONCO, a randomized double-blind multicenter trial, evaluated the efficacy and safety of the ultra-LMWH semuloparin for prevention of CAT in 3,212 patients with metastatic or locally advanced solid malignancy receiving chemotherapy. Semuloparin significantly reduced the incidence of CAT (1.2% and 3.4% in the semuloparin and placebo groups, respectively) without a significant effect on major bleeding (2.8% and 2.0% in the semuloparin and placebo groups, respectively).

CONKO-004, a prospective randomized trial, evaluated enoxaparin prophylaxis in 312 patients with advanced pancreatic cancer starting chemotherapy. Enoxaparin was prescribed at 1 mg/kg once daily for 3 months followed by 40 mg daily thereafter until disease progression. Enoxaparin reduced the incidence of VTEs (6.4% and 15.1% in the enoxaparin and observation groups, respectively) without an increase in major bleeding. Some limitations regarding CONKO-004 are worth noting. The open non-blinded design may have led to bias. Asymptomatic VTEs found on routine imaging were excluded despite their clinical relevance. Moreover, the study was stopped early after the required number of VTE events for the primary outcome was reached and may therefore have been underpowered for overall survival (OS; secondary endpoint).

There was no significant impact on OS with the use of CAT prophylaxis in PROTECHT (nadroparin), SAVO-ONCO (semuloparin), or CONKO-004 (enoxaparin) trials. Of note, achieving a survival advantage with LMWH prophylaxis in patients with cancer has been challenging. The FAMOUS was a randomized, placebo-controlled, double-blind study to evaluate the effect of VTE prophylaxis with dalteparin on OS among patients with cancer. Dalteparin did not significantly improve the 1-year survival rate, perhaps because there was a high early mortality rate in patients with advanced cancer randomized to the trial. Of note, the subgroup of patients with cancer with better prognosis who were alive 17 months after randomization had significantly improved OS.

Although VTE prevention trials showed a significant CAT risk reduction, the absolute risk reduction was too low to recommend routine CAT prophylaxis for all ambulatory patients with cancer. A systematic review of 9 randomized clinical trials including 3,538 ambulatory patients with cancer receiving chemotherapy found that LMWH significantly reduced symptomatic CAT (relative risk [RR], 0.62; 95% CI, 0.41–0.93) but with a relatively high number needed to treat (NNT; n=60). Compared with inactive control, LMWH was associated with a non-statistically significant increase in major bleeding (RR, 1.57; 95% CI, 0.69–3.60). This prompted attempts to better identify and target the patients with cancer at highest risk using a validated CAT risk tool.

The CASSINI and AVERT clinical trials assessed CAT prevention in intermediate- and high-risk ambulatory patients with cancer, defined by the Khorana score, using rivaroxaban and apixaban, respectively. In the CASSINI trial, intermediate- and high-risk ambulatory patients with cancer (Khorana score ≥2), were randomly assigned to receive rivaroxaban (10 mg daily) or placebo daily for up to 180 days. The incidence of CAT was lower in the rivaroxaban (2.6%) versus placebo group (6.4%) in the prespecified intervention period analysis (hazard ratio [HR], 0.40; 95% CI, 0.20–0.80), with low incidence of major bleeding (2.0% and 1.0%, respectively [HR, 1.96; 95% CI, 0.59–6.49]). In the AVERT trial, intermediate- and high-risk ambulatory patients with cancer (Khorana score ≥2), were randomly assigned to receive apixaban (2.5 mg twice daily) or placebo daily for up to 180 days. The incidence of CAT was also lower with the apixaban group (4.2% vs 10.2% with placebo; HR, 0.41; 95% CI, 0.26–0.65; P < .001). During the treatment period, major bleeding occurred in 2.1% in the apixaban group and 1.1% in the placebo group (HR, 1.89; 95% CI, 0.39–9.24).

The CASSINI and AVERT trials showed compelling evidence of the safety and efficacy of DOACs for CAT prevention, with a low incidence of major bleeding. However, it is worth mentioning that even with selecting intermediate- and high-risk ambulatory patients with cancer using Khorana score, the NNT remained relatively
high (n=40). Current NCCN Guidelines include rivaroxaban and apixaban in the outpatient primary prophylaxis guidelines for intermediate- and high-risk patients with cancer (Figure 1).

The cost of DOACs is overestimated. Currently, we do not monitor the anticoagulant effect of DOACs, and the reduction in CAT recurrences reduces the overall cost of medical care, easily compensating for the difference in cost between DOACs and other anticoagulants. Li et al showed that in patients with cancer at intermediate to high risk for CAT, thromboprophylaxis with low-dose rivaroxaban and apixaban for 6 months, compared with placebo, was associated with 32 per 1,000 fewer CAT but 11 per 1,000 more major bleeding episodes over a lifetime. The incremental cost and quality-adjusted life-year (QALY) increases were $1,445 and 0.12, respectively, with an Institute for Clinical and Economic Review (ICER) of $11,947 per QALY gained. This strategy was 94% cost-effective at the threshold of $50,000 per QALY gained. Selection of patients with cancer with Khorana scores of ≥3 yielded the greatest value, with an ICER of $5,794 per QALY gained.

**NCCN Guidelines Recommendation**
- Consider outpatient thromboprophylaxis for up to 6 months with LMWH or oral anticoagulant (rivaroxaban or apixaban) for intermediate- or high-risk patients with cancer (Khorana score of ≥2). Continuing primary thromboprophylaxis beyond 6 months should only be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy, to ensure a continued favorable risk/benefit profile.

**CAT Prevention in Patients With Multiple Myeloma**
Patients with multiple myeloma (MM) are at an increased risk of CAT, which is associated with significantly poorer survival. Thrombosis risk among patients with MM receiving immunomodulatory drug (IMiD) monotherapy is approximately 3% to 4% but could increase up to 26% with the addition of high-dose glucocorticoids, anthracyclines, or erythropoietin. It is worth noting that the rate of adherence to the NCCN Guidelines for CAT in patients with newly diagnosed MM is only 66%. Current recommendations for CAT prophylaxis in MM are based on limited available data. The AVERT trial included only 2.6% patients with MM, whereas patients with MM were excluded from the CASSINI trial. Two clinical RAMs predicting CAT risk among patients with MM are currently available. Sanfilippo et al published in 2019 the IMPEDE VTE risk clinical score for patients with MM (Table 2). The Veterans Administration Central Cancer Registry (n=4,446) was used to derive a RAM, then data from the SEER-Medicare database was used to externally validate the model (Table 2). Three risk groups were identified, and the respective 6-month cumulative incidence of VTE following treatment initiation was 3.3% for the low-risk group (score ≤3), 8.3% for intermediate-risk group (score of 4–7), and 15.2% for the high-risk group (score ≥8).

Li et al also derived and validated a new RAM for patients with newly diagnosed MM specifically receiving IMiDs. The SEER-Medicare database (n=2,397) was used to derive a RAM and then data from the Veterans Health Administration database (n=1,251) were used to externally validate the model. Five variables were included in the final RAM, named the “SAVED” score (Table 2). Patients were grouped into either low- or high-risk using this RAM, and the HRs reported for high versus low VTE risk were 1.85 (P<.01) and 1.98 (P<.01), respectively. The limitations of both scoring systems include the absence of prospective validation and lack of distinction between patients with newly diagnosed versus relapsed/refractory MM.
NCCN Guidelines Recommendation

- High-risk patients (SAVED ≥2 or IMPEDE VTE ≥4 score) should receive prophylactic-dose LMWH, apixaban (2.5 mg twice daily), rivaroxaban (10 mg daily), fondaparinux (2.5 mg daily) or warfarin (international normalized ratio, 2.0–3.0), whereas low-risk patients (SAVED <2 or IMPEDE VTE ≤3 score) should receive aspirin or no prophylaxis (Figure 2)\(^{35}\)

**CAT Prevention in Patients With Myeloproliferative Neoplasms**

Thrombosis is prevalent across myeloproliferative neoplasms and has significant impact on morbidity and mortality. The pooled prevalence of overall thrombosis is 28.6%, 20.7%, and 9.5% for patients with newly diagnosed polycythemia vera (PV), essential thrombocytosis (ET), and myelofibrosis, respectively.\(^{36}\)

PV has the highest risk of venous and arterial thrombosis. Thrombosis can even precede the PV diagnosis by many years.\(^{37}\) The double-blind randomized ECLAP trial assessed the use of low-dose aspirin in preventing thrombotic complications in patients with PV.\(^{38}\) Results showed that aspirin safely reduced the risk of the combined endpoint of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (RR, 0.41; 95% CI, 0.15–1.15; \(P = .09\)) and the risk of the combined endpoint of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes (RR, 0.40; 95% CI, 0.18–0.91; \(P = .03\)).\(^{38}\)

In patients with PV, targeting hematocrit levels to <45% can also lower the risk of thrombosis. The CYTOPV trial randomized 365 adults with PV to either more intensive treatment (hematocrit <45%) or less intensive treatment (hematocrit 45%–50%).\(^{39}\) Targeting a hematocrit level <45% significantly reduced the composite primary endpoint of time until death from cardiovascular causes or major thrombotic events (HR in the high hematocrit group, 3.91; 95% CI, 1.45–10.53; \(P = .007\)).\(^{39}\)

Cytoreductive therapy with hydroxyurea is currently recommended for high-risk patients with PV (age >60 years or prior history of thrombosis),\(^{40}\) a recommendation largely extrapolated from studies involving patients with ET.\(^{41}\)

Treatment in ET is primarily indicated to prevent thrombotic complications. Prior history of thrombosis, age >60 years, and \(JAK2\) mutation are known risk factors for thrombosis. Recently, leukocytosis was also

**Table 2. CAT Risk Assessment Models for Patients With MM Receiving IMiDs**

<table>
<thead>
<tr>
<th>IMPEDE VTE Score</th>
<th>SAVED Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin, 40 mg SC once daily</td>
<td>40 mg SC once daily</td>
</tr>
<tr>
<td>Dalteparin, 5,000 units SC daily</td>
<td>5,000 units SC daily</td>
</tr>
<tr>
<td>Warfarin (INR 2–3)</td>
<td>INR 2–3</td>
</tr>
<tr>
<td>Apixaban, 2.5 mg PO every 12 hr</td>
<td>every 12 hr</td>
</tr>
<tr>
<td>Fondaparinux, 2.5 mg daily</td>
<td>2.5 mg daily</td>
</tr>
<tr>
<td>Rivaroxiban, 10 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>No intervention</td>
<td></td>
</tr>
<tr>
<td>Aspirin, 81–325 mg PO daily</td>
<td>81–325 mg PO daily</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CAT, cancer-associated thrombosis; IMiD, immunomodulatory drug; LMWH, low-molecular-weight heparin; MM, multiple myeloma; VTE, venous thromboembolism.

shown to be associated with thrombosis in patients with ET.\textsuperscript{42} The revised International Prognostic Score for Thrombosis in ET (IPSET-thrombosis) classifies patients with ET into 4 thrombotic risk categories: very low (no adverse features), low (presence of JAK2 V617F mutation only), intermediate (age >60 years only), and high (history of thrombosis or age >60 years and JAK2 V617F mutation).\textsuperscript{43} NCCN currently recommends a risk adaptive therapy for patients with ET (Figure 3).\textsuperscript{44} Patients with ET with refractory vasomotor symptoms or high cardiovascular risks might benefit from twice-daily aspirin, but this must be weighed against risk of bleeding.\textsuperscript{45,46} Target platelet goal is $600 \times 10^9$/L when cytoreductive therapy is used for high-risk patients with ET.\textsuperscript{41}

**NCCN Guidelines Recommendations**

- NCCN recommends aspirin plus phlebotomy (hematocrit <45%) for low-risk PV, and the addition of cytoreductive therapy for high-risk PV (Figure 3).\textsuperscript{44}
- NCCN recommends observation alone for very low risk ET, aspirin for low- and intermediate-risk ET, and cytoreductive therapy plus aspirin for high-risk ET (Figure 3).\textsuperscript{44}

**Selecting Anticoagulants for CAT Prevention**

Patients with upper gastrointestinal malignancy and potentially genitourinary malignancies might have an increased bleeding risk with DOACs, thus prophylactic LMWH is preferred.\textsuperscript{47} In a post hoc analysis of the CASSINI trial, the rate of major bleeding among patients with gastric/gastroesophageal junction was increased compared with patients with other malignancies.\textsuperscript{48} In a post hoc analysis of the AVERT trial, patients with pancreatic/hepatobiliary cancer had a nonsignificant increased risk of major bleeding complications, whereas no major bleeding was observed among patients with upper gastrointestinal malignancies.\textsuperscript{49} However, it is worth noting that the AVERT trial included only a small proportion of patients with gastric tumors (8.6% in the apixaban arm and 6.7% in the placebo arm).

Drug–drug interaction should always be checked prior to using a DOAC. For patients with creatinine clearance <30 mL/min/1.73 m$^2$,\textsuperscript{50} DOACs should not be used, whereas LMWH could be used at 30 mg subcutaneously once daily. LMWH is the agent of choice for patients with morbid obesity. LMWH dose fixing (dose “capping”) is linked to high thrombosis rates. A weight-based LMWH dose of 0.5 mg/kg/d is a reasonable consideration in patients with morbid obesity.\textsuperscript{50} Absolute contraindications include active bleeding, thrombocytopenia (platelets <30,000–50,000 $\times 10^9$/L), underlying bleeding disorder (eg, hemophilia, von Willebrand disease, baseline prolonged prothrombin time or partial prothrombin time [excluding lupus anticoagulant]), and high risk for falls.

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**Figure 3.** CAT prevention algorithm for patients with PV and ET.

**Abbreviations:** CAT, cancer-associated thrombosis; ET, essential thrombocythemia; PV, polycythemia vera.

Prevention of Cancer-Associated Thrombosis

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