

# Prevention and treatment of cancer-associated thrombosis

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## ABSTRACT

Cancer is a hypercoagulable state with an associated increased risk of venous thromboembolism (VTE) that is further amplified in individuals who undergo chemotherapy. Compared with patients having cancer alone or VTE alone, patients who develop cancer-associated VTE have a significantly poorer prognosis. The risks of recurrent VTE despite appropriate anticoagulation therapy and of bleeding are also higher in patients with cancer than in those without. For those reasons, the prevention and appropriate management of cancer-associated thrombosis is of paramount importance. Although low-molecular-weight heparin has been the standard of care for the prevention and treatment of cancer-associated thrombosis, direct oral anticoagulants are increasingly being adopted as an effective and safe alternative.

**Key Words** Venous thromboembolism, anticoagulation, direct oral anticoagulants, thromboprophylaxis, cancer-associated thrombosis

*Curr Oncol.* 2020 October 27(5):275–278

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## INTRODUCTION

Cancer-associated thrombosis is a major cause of morbidity and mortality in patients with malignancy. Thromboembolism is the 2nd leading cause of death in patients with cancer, with the most common thrombotic complication being venous thromboembolism (VTE)<sup>1–5</sup>. Although deep-vein thrombosis (DVT) and pulmonary embolism (PE) are the most frequent clinical presentations of VTE, thrombosis in other vascular structures, such as the upper limb and splanchnic veins, also commonly occurs in the setting of malignancy<sup>6</sup>. In patients with cancer compared with those without, the risk of developing VTE is increased by a factor in the range of 4–7<sup>1</sup>. Aside from individual patient-related risk factors, tumour-related risk factors such as tumour type, tumour stage and grade, and the anticancer treatments being delivered also contribute to heightened VTE risk<sup>7</sup>. It is estimated that up to 20% of patients with cancer are affected by VTE, with the highest risk periods being those associated with hospitalizations and the development of metastatic disease<sup>8,9</sup>.

Compared with patients having cancer alone or VTE alone, patients who develop cancer-associated VTE have a significantly poorer prognosis<sup>3</sup>. The risks of recurrent VTE despite appropriate anticoagulation therapy and of bleeding are also higher for patients with cancer than for those without<sup>4</sup>. Thus, the management of thrombotic and

bleeding complications have to be delicately balanced in patients with cancer. Although low-molecular-weight heparin (LMWH) has been the standard of care for the prevention and treatment of cancer-associated VTE for many years, direct oral anticoagulants (DOACs) are increasingly being used after several landmark trials showed them to be effective and safe options. In the present review, we outline two scenarios of patients with cancer-associated VTE and critically assess the evidence and recent advances that guide treatment decisions.

## CASE STUDIES

### Case 1

#### Presentation

A 50-year-old man with a recent diagnosis of stage III colonic adenocarcinoma is referred for the management of an isolated subsegmental PE in the right lower lobe, found

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incidentally on his staging computed tomography examination. He reports no dyspnea, chest pain, or hemoptysis. He recounts a 3-month history of weight loss and intermittent small-volume rectal bleeding. Although he reports no lower limb symptoms, bilateral lower limb compression ultrasonography reveals an occlusive thrombus within his left posterior tibial vein. His current body weight is 73 kg, and he has a creatinine clearance of 70 mL/min. He is scheduled for a left hemicolectomy in 3 weeks, followed by adjuvant chemotherapy postoperatively. Is anticoagulation treatment warranted? And if so, which anticoagulant should be prescribed?

### Evidence

Approximately 50% of all VTEs diagnosed in patients with cancer are found incidentally on imaging performed for cancer staging, treatment response, or follow-up<sup>10</sup>. The prevalences of incidental pulmonary emboli and of incidental lower-limb DVTs have been reported to range, respectively, between 1% and 15% and between 1% and 7% in this patient population<sup>11</sup>. Although the clinical relevance of an isolated subsegmental PE in the general population is unclear, studies have shown that, despite application of anticoagulation therapy, the risk of recurrent VTE in cancer patients with subsegmental PE appears to be comparable to that in patients with more proximal clots<sup>12,13</sup>. Similarly, distal DVT has also been shown to be associated with poorer prognosis in patients with cancer, given similar rates of VTE recurrence, bleeding, and mortality<sup>14,15</sup>. Based on the increased risk of VTE recurrence, current guidelines suggest a course of anticoagulation to be preferable to a more conservative approach of watchful waiting for the management of incidental subsegmental PE with concomitant DVT<sup>16</sup>.

Low-molecular-weight heparin has been the mainstay of treatment for acute cancer-associated VTE for many years, given that several studies showed it to be associated with a lower risk of VTE recurrence without a significant increase in major bleeding in a comparison with vitamin K antagonists<sup>17</sup>. The advantages of LMWH over vitamin K antagonists include reliable delivery of anticoagulation that is not affected by dietary intake, fewer drug–drug interactions, and the ability to adjust and withhold doses in the setting of acute cytopenias. However, the need for daily injections and the associated costs often deter patients from persisting with LMWH for the recommended duration of treatment<sup>18</sup>.

Recently, four pivotal randomized trials comparing DOACs with LMWH for the acute treatment of cancer-associated VTE were published.

The HOKUSAI VTE cancer trial compared edoxaban with dalteparin for the treatment of acute VTE in 1046 patients with cancer. Edoxaban was shown to be noninferior to dalteparin for the primary outcome of recurrent VTE or major bleeding episodes. Compared with dalteparin, edoxaban seems to be associated with a lower rate of VTE recurrence [hazard ratio (HR): 0.71; 95% confidence interval (CI): 0.48 to 1.06]; however, at 12 months of follow-up, it was also associated with a significantly higher rate of major bleeding (HR: 1.77; 95% CI: 1.03 to 3.04) and a potentially higher rate of clinically relevant non-major bleeding (HR: 1.38; 95% CI: 0.98 to 1.94)<sup>19</sup>.

The SELECT-D study compared rivaroxaban with dalteparin for the treatment of acute VTE in 406 cancer patients. At 6 months of follow-up, the incidence of VTE recurrence was lower in patients treated with rivaroxaban than in those treated with dalteparin (HR: 0.43; 95% CI: 0.19 to 0.99), but rivaroxaban seemed to be associated with a higher incidence of major bleeding (HR: 1.83; 95% CI: 0.68 to 4.96)<sup>20</sup>. Major gastrointestinal bleeding, predominantly in patients with gastrointestinal cancers, was noted to be more prominent in patients randomized to anticoagulation with DOACs in both the HOKUSAI VTE and SELECT-D trials.

The ADAM VTE trial compared apixaban with dalteparin in 300 cancer patients with acute VTE. Recurrent VTE occurred in 0.7% of the apixaban group and in 6.3% of the dalteparin group. Major bleeding events occurred at rates of 0% in the apixaban group and 1.4% in the dalteparin group<sup>21</sup>.

The Carvaggio trial also compared apixaban with dalteparin for the treatment of acute VTE in 1175 cancer patients. Apixaban was noninferior to dalteparin in preventing recurrent VTE, with a lower rate of recurrent events in patients treated with apixaban (HR: 0.63; 95% CI: 0.37 to 1.07;  $p < 0.001$  for noninferiority) and similar rates of major bleeding in the two cohorts (HR: 0.82; 95% CI: 0.40 to 1.69)<sup>22</sup>.

### Therapy Choice

Given that the patient has an unresected colonic carcinoma with ongoing modest bleeding, he was started on therapeutic anticoagulation with dalteparin at 200 IU/kg daily, with a dose reduction of 75% after 1 month with no major bleeding complications. Given the low thrombotic burden, this patient's treating physician opted to briefly interrupt the anticoagulation perioperatively without insertion of an inferior vena cava filter. After 3 months, because of needle fatigue, the patient was switched to apixaban 5 mg twice daily; he remained on that dose for a minimum of 6 months and until completion of his chemotherapy.

## Case 2

### Presentation

A 74-year-old woman has been referred by her medical oncologist for advice about outpatient VTE prophylaxis. She has just been discharged from hospital after being diagnosed with metastatic pancreatic adenocarcinoma, with a plan to start gemcitabine monotherapy in the coming weeks. Her only medication is pancrelipase with meals. Her weight today is 62 kg. Her bloodwork shows hemoglobin 100 g/L, white cell count  $13.5 \times 10^9/L$ , platelet count  $200 \times 10^9/L$ , and creatinine clearance 50 mL/min. Her Khorana score is 3. Should this patient receive outpatient VTE prophylaxis?

### Evidence

Thromboprophylaxis is not routinely offered to all outpatients with cancer. However, the 2019 American Society of Clinical Oncology guideline recommends that high-risk outpatients with cancer (those with a Khorana score of 2 or greater before starting systemic chemotherapy) be offered thromboprophylaxis with rivaroxaban, apixaban, or LMWH when no significant bleeding risk factors or drug–drug interactions are evident<sup>23</sup>.

Compared with no thromboprophylaxis, LMWH significantly reduces the incidence of symptomatic VTE (relative risk: 0.54; 95% CI: 0.38 to 0.75) in ambulatory patients with cancer who are receiving chemotherapy. However, LMWH is associated with a risk of major bleeding events, albeit not a statistically significant one (relative risk: 1.44; 95% CI: 0.98 to 2.11)<sup>24</sup>.

More recently, two randomized double-blind placebo-controlled trials evaluated the use of DOACs for thromboprophylaxis in high-risk ambulatory patients with cancer.

The CASSINI study compared rivaroxaban 10 mg daily with placebo for thromboprophylaxis in 841 ambulatory cancer patients who were starting antineoplastic therapy. In the intention-to-treat analysis, the primary efficacy outcome (a composite of incidental or symptomatic DVT or PE, upper limb DVT, distal DVTs, or VTE-related death) reached 6.0% in the rivaroxaban group and 8.8% in the placebo group (HR: 0.66; 95% CI: 0.40 to 1.09). The main safety outcome of major bleeding occurred in 2.0% of the rivaroxaban group and in 1.0% of the placebo group (HR: 1.96; 95% CI: 0.59 to 6.49)<sup>25</sup>.

The AVERT study assessed apixaban 2.5 mg twice daily against placebo for thromboprophylaxis in 563 ambulatory cancer patients who were starting systemic chemotherapy. In the modified intention-to-treat analysis, the primary efficacy outcome (a composite of incidental or symptomatic PE or symptomatic proximal DVT- or VTE-related death) occurred in 4.2% of the apixaban group and in 10.2% of the placebo group (HR: 0.41; 95% CI: 0.26 to 0.65), with major bleeding occurring in 3.5% of the apixaban group and 1.8% of the placebo group (HR: 2.00; 95% CI: 1.01 to 3.95)<sup>26</sup>. In CASSINI, patients with pancreatic and gastroesophageal cancers made up a larger proportion of the population; in AVERT, patients with hematologic (lymphoma, multiple myeloma) and gynecologic cancers constituted a larger proportion of the population.

## Therapy Choice

After discussion with the patient, she was started on rivaroxaban 10 mg daily for outpatient VTE prophylaxis per patient preference.

## SUMMARY

Given their convenience, efficacy, and safety in most patients, DOACs are increasingly being used for the prevention and treatment of cancer-associated VTE. The type of tumour, the risk of bleeding, potential drug–drug interactions, and patient preference should all be considered when starting a patient on anticoagulation treatment, and the decision should be regularly reviewed while the patient remains on anticoagulation.

## ACKNOWLEDGMENTS

MC is the recipient of a Tier 2 Research Chair from the Department of Medicine and University of Ottawa in cancer-associated thrombosis.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: MC has received research funding from Bristol Myers

Squibb, Leo Pharma, and Pfizer, and honoraria from Bayer, Bristol Myers Squibb, Leo Pharma, Pfizer, Sanofi, and Servier. SN has no conflicts to disclose.

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