A Review of the Past, Present and Future of Cancer-associated Thrombosis Management

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Venous thromboembolism (VTE) can have a significant impact on the management, quality of life and mortality of patients with cancer. VTE occurs in 5–20% of patients with cancer, and malignancy is associated with up to 25% of all VTE. It is the second leading cause of death in ambulatory patients with cancer who are receiving chemotherapy. Increased rates of cancer-associated thrombosis are attributed to improved patient survival, increased awareness, surgery, antineoplastic treatments and the use of central venous access devices. Many factors influence cancer-associated thrombosis risk and are broadly categorized into patient-related, cancer-related and treatment-related risks. Direct-acting oral anticoagulants have shown themselves to be at least as effective in preventing recurrent VTE in patients with cancer with symptomatic and incidental VTE. This has led to a change in treatment paradigms so that direct-acting oral anticoagulants are now considered first-line agents in appropriately selected patients. In this article, we review the prior and recent landmark studies that have directed the treatment of cancer-associated thrombosis, and discuss specific factors that affect management as well as future treatment considerations.

Keywords

Direct-acting oral anticoagulants, apixaban, edoxaban, rivaroxaban, low-molecular-weight heparin, anticoagulants, pulmonary embolism, venous thromboembolism, deep vein thrombosis, risk factors

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In this article, we review prior and recent landmark studies that have directed the treatment of cancer-associated thrombosis (CAT), discuss specific factors that influence anticoagulant choice, and explore ongoing trials that may impact treatment in the future. Older data estimated less than 1% of patients with malignancy developed venous thromboembolism (VTE), but more recent data suggest VTE occurs in 5–20% of patients with cancer, and malignancy is associated with up to 25% of all VTE.[1–3] The risk of any VTE in cancer patients is four to seven times higher than non-cancer patients, and the incidence of pulmonary embolism (PE) in hospitalized patients with cancer is twice that of hospitalized non-cancer patients.[3,4] Patients with cancer are at a threefold higher risk of recurrent VTE compared with patients without malignancy, and a recent cohort study showed the risk of VTE was 11 times higher at 6 months after cancer diagnosis.[5]

During the month following the index VTE, patients with cancer are at their highest risk for both recurrent VTE and bleeding events.[6] The increase in CAT is attributed to improved patient survival, increased CAT awareness, surgical resections, antineoplastic treatments and the use of central venous access devices.[7,8] Many factors influence CAT risk; these are broadly categorized into patient-related, cancer-related and treatment-related risks. Patient-related factors include age, mobility, functional status, tobacco use, obesity, parenteral nutrition requirements and medical comorbidities, such as heart failure, renal disease, pulmonary disease, and infection and its complications. Patients with prior thromboembolic events are also at increased risk of recurrent VTE, even while on anticoagulation.[8,9]

Cancer-related thrombotic risks include type of malignancy and disease stage. Malignancy induces a pro-thrombotic state attributable to increased leukocytosis, thrombocytosis, expression of tissue factor, phospholipids and inflammatory markers.[10] Malignancies associated with the greatest risk of VTE include brain, pancreatic and gastric, followed by other gastrointestinal (GI) cancers, lung, ovarian, testicular, renal and bladder cancers.[10,11] Haematological malignancies, specifically multiple myeloma, acute leukaemia and lymphoma, are also associated with thrombosis.[9] A study of patients with cancer and VTE from the REITE registry compared treatment outcomes among solid and haematological malignancies.[12] Haematological malignancies were divided into three subgroups: lymphoma, multiple myeloma and other haematological cancers. The most common solid cancers were lung, colorectal and breast. The authors found haematological malignancies were less likely to develop PE than isolated deep vein thrombosis (DVT) and more likely to have upper extremity DVT, although this was often catheter associated.[12] Those with haematological CAT also had significantly reduced rates of symptomatic recurrent VTE, major bleeding and all-cause mortality, compared with patients with solid tumours. In particular, the multiple myeloma subgroup had less than half the rate of recurrent VTE or major bleeding and less than one-third of the mortality rate when compared with the solid tumour subgroup. These data suggest that patients

Table 1: Clinical guideline recommendations for anticoagulants and length of therapy in the treatment of cancer-associated thrombosis

Guideline	Initiation (up to 10 days)	Maintenance (up to 6 months)	Long-term (beyond 6 months)
ACCP[33] (2021)	DOACs (apixaban, edoxaban, rivaroxaban) over LMWH • Apixaban may be preferred in patients with luminal GI malignancy		DOACs • No scheduled stop date with periodic assessments • Can use VKA if DOACs are contraindicated
ASCO[34] (2020)	LMWH, UFH, fondaparinux or rivaroxaban • LMWH recommended over fondaparinux	LMWH, edoxaban or rivaroxaban	LMWH, DOACs or VKAs • Patients with active cancer, metastatic disease or receiving chemotherapy • Intermittent assessment of risk–benefit ratio
ASH[2] (2021)	Apixaban, rivaroxaban or LMWH • LMWH recommended over fondaparinux	DOACs (apixaban, edoxaban or rivaroxaban) over LMWH • Up to 6 months	DOACs or LMWH • Indefinite therapy, and periodic re-evaluation for those with active cancer
ITAC[7] (2019)	LMWH • Can use rivaroxaban/edoxaban in patients without a high risk of GI/GU bleeding • UFH or fondaparinux can be used if LMWH or DOACs are contraindicated	LMWH or DOACs • Use caution with DOACs and GI tract malignancy	LMWH or DOACs • Should be used for minimum of 6 months based on individual evaluation
NCCN[9] (2021)	LMWH, edoxaban or rivaroxaban	LMWH, edoxaban or rivaroxaban • For minimum of 3 months	LMWH, edoxaban or rivaroxaban • Patients with active cancer, undergoing treatment or with a persistent risk factor • Based on clinical judgment

ACCP = Advanced Critical Care Practitioners; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; DOAC = direct-acting oral anticoagulant; GI = gastrointestinal; GU = genitourinary; ITAC = International Initiative on Thrombosis and Cancer; LMWH = low-molecular-weight heparin; NCCN = National Comprehensive Cancer Network; UFH = unfractionated heparin; VKA = vitamin K antagonists.

with haematological CAT have better outcomes while on treatment compared with those with solid tumours.[12] Treatment-associated risks include medical therapies, such as chemotherapy, endocrine therapy, angiogenesis inhibitors, immunotherapy, protein kinase inhibitors, transfusions and cell-line stimulating agents, which have all been associated with VTE.[8,9] Chemotherapy is reported to increase thrombotic events by almost seven times compared with patients with cancer not on chemotherapy.[1,8,13] Other treatment modalities (e.g. surgery) and treatment-associated factors (e.g. hospitalization and central venous catheters) also increase VTE risk in patients with cancer.[8,13]

Mortality in patients with cancer and venous thromboembolism

The second leading cause of death in ambulatory patients with cancer receiving chemotherapy is VTE.[8,13,14] CAT is a significant predictor of death, which is independent of other factors such as age, race and stage of cancer. The 1-year survival rates of cancer patients with VTE have been noted to be one-third of those without VTE.[15,16]

Cancer patients presenting with PE and treated with therapeutic anticoagulation suffer from fatal PE at four times the rate of fatal bleeding, with 88% of fatal PE occurring in the first 30 days.[17] After the first 30 days, mortality rates associated with recurrent PE reach a maximum at approximately 3 months after the initial event. Fatal bleeding has been found to be more frequent after the first 30 days and can occur up to a year after the initial PE.[17,18] A prospective study of post-surgical patients with cancer found that death due to VTE accounted for nearly half of all mortality in the 30 days following surgery.[19]

Unfractionated heparin versus low-molecular-weight heparin

For initial VTE management, low-molecular-weight heparin (LMWH) is preferred over fondaparinux and unfractionated heparin (UFH) due to ease of use and reductions in mortality, recurrent VTE and major bleeding.[2,20] UFH is useful in peri-procedural settings and in those with renal insufficiency with a creatinine clearance <30 mL/min or severe obesity.[2,20] LMWH is preferred over UFH due to decreased rates of heparin-induced thrombocytopenia (HIT).[2,20] For those with a history of HIT, fondaparinux may be used.[21] A review of the use of direct-acting oral anticoagulants (DOACs) in HIT showed that while rivaroxaban has been the most studied, DOACs, as a class, are efficacious in preventing new and recurrent thrombosis, with low rates of bleeding.[22–27] The 2018 guidelines from the American Society of Hematology state that DOACs are reasonable for the treatment of HIT and for prophylaxis in patients with remote HIT who are clinically stable and have average bleeding risk.[21]

Low-molecular-weight heparin versus vitamin K antagonist

Trials comparing LMWH to vitamin K antagonists (VKAs) have shown superiority with LMWH in preventing recurrent VTE with similar or improved major bleeding events.[28–31] The CLOT, LITE, ONCENOX and CATCH studies all showed an approximately 7% VTE recurrence rate with LMWH compared with 10–16% with VKA.[23–26] LMWH also had reduced or similar bleeding rates compared with VKA.[28–31] This led to LMWH being the standard of care for treatment of CAT until very recently.[2,24,32–35] Major clinical guideline recommendations for anticoagulants in the treatment of CAT are listed in *Table 1*.[2,7,9,33,34]

Factor Xa inhibitors for cancer-associated thrombosis

Only five randomized trials prospectively compared the efficacy and safety of factor Xa-inhibiting DOACs to LMWH for CAT treatment.[24,32–40] There are data from *post-hoc* analyses of other DOAC trials; however, these were not conducted nor powered to evaluate the treatment of CAT and, therefore, were not included in this review. It is important to note that while these trials and major guidelines use the term DOAC, they are

only referencing factor Xa inhibitors. The trials are the following: Hokusai VTE Cancer (Cancer venous thromboembolism [VTE]; ClinicalTrials.gov Identifier: NCT02073682), SELECT-D (Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial; ISRCTN number: ISRCTN86712308), the ADAM VTE trial (Apixaban or dalteparin in reducing blood clots in patients with cancer related venous thromboembolism; ClinicalTrials.gov identifier: NCT02585713), Caravaggio (Apixaban for the treatment of venous thromboembolism in patients with cancer [CARAVAGGIO]; ClinicalTrials.gov identifier: NCT03045406) and CASTA DIVA (Cancer associated thrombosis, a pilot treatment study using rivaroxaban [CASTA-DIVA]; ClinicalTrials.gov identifier: NCT02746185).[24,32–40] There has not been a published study prospectively comparing dabigatran to LMWH for the treatment of CAT.

Hokusai VTE Cancer

The Hokusai VTE Cancer trial was an open-label, non-inferiority trial of 1,050 patients with cancer (ClinicalTrials.gov identifier: NCT02073682).[36] Patients were randomized to receive edoxaban or dalteparin for 6 to 12 months for the treatment of acute symptomatic or incidental VTE. Edoxaban was found to be non-inferior to dalteparin with respect to the composite primary outcome of recurrent VTE and major bleeding (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.7–1.36).[36] All-cause mortality was similar between both edoxaban and dalteparin, as well as deaths related to VTE or bleeding.[36] When individual outcomes were examined, edoxaban had a non-significant reduction in VTE recurrence (HR 0.71, 95% CI 0.48–1.06) and a statistically significant increase in major bleeding (HR 1.77, 95% CI 1.03–3.04) but not in clinically relevant non-major bleeding (CRNMB) (HR 1.38, 95% C: 0.98–1.94).[36] The increased risk of major bleeding was notable for patients with GI cancers.[36] This was later confirmed by a *post-hoc* analysis that showed the increased major bleeding was mostly upper GI bleeding and occurred among all types of GI cancers (HR 4.0, 95% CI 1.5–10.6).[41] GI bleeding occurred mostly in those with non-resected tumours, but upper GI bleeding also occurred in those who had tumour resections, including for colorectal cancer.[32,41] Further investigation to elucidate risk factors for GI bleeding found significantly increased bleeding in patients with advanced cancer (metastatic or locally advanced) (odds ratio [OR] 3.6, 95% CI 1.01–12.6) and haemoglobin <10 g/dL (OR 4.8, 95% CI 1.5–16.0).[42] Patients with resected GI tumours had a non-significant decrease in GI bleeding risk.[42] This suggests that non-metastatic GI cancer patients without anaemia may be at lower risk for GI bleeding and suitable for treatment with edoxaban.

A limitation of the Hokusai VTE Cancer study is its design as an open-label study. To overcome this limitation, all events had to be adjudicated by a separate blinded committee.[36] Another limitation was that the primary outcome occurred less than expected, but non-inferiority could still be determined.[36] Finally, results may have also been biased because the median treatment duration with dalteparin was approximately 1 month shorter than in the edoxaban group duration. This difference in treatment duration was attributed to dalteparin administration via subcutaneous injection compared with edoxaban's easier oral administration.[36]

SELECT-D

The SELECT-D trial was another, open-label, randomized, multicentre trial of 406 patients with active cancer and symptomatic lower extremity DVT or symptomatic/incidental PE who received rivaroxaban or dalteparin for 6 months.[37] Rivaroxaban showed a statistically significant reduction in the primary outcome of recurrent VTE at 6 months compared with dalteparin (HR 0.43, 95% CI 0.19–0.99). Major bleeding was non-significantly higher in the rivaroxaban arm (HR 1.83, 95% CI 0.68–4.96).[37] Prior to completion, the data and safety monitoring committee found increased major bleeding in those with oesophageal or gastro-oesophageal cancers enrolled in the rivaroxaban arm, so enrolment was stopped as a precaution.[37] CRNMB was significantly higher among patients in the rivaroxaban arm compared with the dalteparin arm (HR 3.76, 95% CI 1.63–8.69), particularly those with bladder and colorectal cancers.[37] Despite increased bleeding events with rivaroxaban, survival was 75% in the rivaroxaban arm and 70% in the dalteparin arm.[37] Limitations of this study include its open-label design and the fact that, while it set out to study treatment beyond 6 months, it could not enrol the number of patients needed.

ADAM VTE

The ADAM VTE trial randomized 300 cancer patients with acute symptomatic or incidental VTE to receive apixaban or dalteparin for 6 months (ClinicalTrials.gov identifier: NCT02585713).[38] This trial was designed to determine superiority, with the primary outcome of major bleeding. It found extremely low rates of major bleeding with both apixaban and dalteparin, 0% versus 1.4%, respectively (HR not estimable).[38] These bleeding rates were lower than those of the other DOAC studies: edoxaban (6.9%) and rivaroxaban (4%).[36,37] The composite of major bleeding and CRNMB was also low but not significantly different between the apixaban and dalteparin arms. Additionally, the VTE recurrence rate with apixaban compared with dalteparin was significantly reduced (0.7% versus 6.3%, respectively; HR 0.099, 95% CI 0.013–0.78) and much lower than those seen with edoxaban or rivaroxaban.[36–38]

Overall, apixaban had a lower incidence of recurrent VTE, major bleeding and CRNMB compared with previous trials of LMWH, edoxaban and rivaroxaban. Variations in study design, sample size, patient selection, randomization or management were all considered as possible causes of differences between the Hokusai VTE Cancer, SELECT-D and ADAM VTE trials.[36–38] Uneven distribution of colorectal and lung cancer patients in the treatment arms and lower enrolment of patients with upper GI cancer contributed to ADAM-VTE not meeting the predefined primary outcome.[38,43]

Caravaggio

The Caravaggio trial was a second larger, open-label, randomized, non-inferiority study comparing apixaban with dalteparin in 1,170 active cancer patients treated for PE, DVT or upper extremity thrombosis during a 6-month period (ClinicalTrials.gov identifier: NCT03045406).[39]

Similarly to Hokusai VTE Cancer and SELECT-D trials,[36,37] this study showed apixaban to be non-inferior to dalteparin for the primary outcome of recurrent VTE (HR 0.63, 95% CI 0.37–1.07). Apixaban showed similar rates of major bleeding compared with dalteparin (HR 0.82, 95% CI 0.40–1.69).[39] Major GI and major non-GI bleeding occurred in similar frequencies in both arms, but CRNMB was non-significantly increased with apixaban (HR 1.42, 95% CI 0.88–2.30).[39] Caravaggio showed the increase in CRNMB was a result of GI and genitourinary (GU) bleeding, as seen in Hokusai VTE Cancer and SELECT-D studies, and upper airway bleeding. There was no significant difference in all-cause mortality between apixaban and dalteparin.[39] Similarly to the previous trials mentioned, the open nature of this study was seen as a limitation but was accounted for by having all outcomes assessed by centrally blinded adjudicators. The authors do note that while they did not power the study to make definite conclusions with respect to bleeding and they did not select GI bleeding as a prespecified outcome, apixaban did exhibit a favourable safety profile.

CASTA DIVA

The most recent non-inferiority open-label, randomized clinical trial compared rivaroxaban with dalteparin during a 3-month treatment period in 158 patients with incidental or symptomatic PE, proximal DVT or ilio-caval thrombosis (ClinicalTrials.gov identifier: NCT02746185).[40] Unfortunately, the CASTA DIVA trial did not meet the criteria to show that rivaroxaban was non-inferior. The trial did show numerically fewer recurrent VTE in the rivaroxaban arm compared with dalteparin (6.4% versus 10.1%, respectively). Also, there was no statistically significant difference between rivaroxaban and dalteparin with respect to major bleeding (1.4% versus 3.7%, respectively), composite of major bleeding and CRNMB (12.2% versus 9.8%, respectively) or death from any cause (25.7% versus 23.8%, respectively).[40] While not significant, the CASTA DIVA trial showed similar trends for recurrent VTE and bleeding compared with what was seen in the previous trials.

The inability to meet the primary outcome can be attributed to a few reasons: low enrolment (possibly due to a stricter definition of active cancer and Ottawa score requirement), low numbers of recurrent VTE, higher mortality rate reducing the number of patients for follow-up, and the significant number of patients who did not have the required imaging all led to a lack of statistical power.[40]

Meta-analyses of Hokusai VTE Cancer, SELECT-D, ADAM VTE, Caravaggio and CASTA DIVA

These five randomized controlled trials examining the efficacy and safety of DOACs compared with LMWH for CAT provided varying results with respect to recurrent VTE, major bleeding, CRNMB and subpopulations who are most at risk for bleeding.[36–40] In an effort to better understand their risks and benefits as a drug class, multiple meta-analyses have been published.

The first meta-analysis published looked at recurrent VTE and major bleeding over a 6-month follow-up period. Additionally, CRNMB, major GI and GU bleeding, mortality, fatal bleeding, fatal PE and treatment discontinuation were analysed.[44]

Recurrent VTE rates in the DOAC cohort were significantly lower than rates in the LMWH group (pooled relative risk [RR] 0.62, 95% CI 0.43–0.91). While major bleeding was non-significantly higher in the DOAC arm (RR 1.31, 95% CI 0.83–1.71), a significant increase in CRNMB was seen among patients treated with DOACs (RR 1.65, 95% CI 1.19–2.28).[44] There were no differences in PE-related death, fatal bleeding events, intracranial bleeding or overall mortality between those treated with DOACs and LMWH. Major GU bleeding was significantly increased (RR 4.99, 95% CI 1.08–23.08) while major GI bleeding showed a non-significant increase in the DOAC cohort.[44] This meta-analysis confirmed a significant increase in major bleeding among GI cancer patients treated with edoxaban and rivaroxaban (RR 2.3, 95% CI 1.08–4.88). When looking at non-GI malignancies, there was no difference in major bleeding between these two DOACs and LMWH.[44]

Due to concern for heterogeneity, a second analysis was run including only Hokusai VTE Cancer, SELECT-D and the Caravaggio trials. This also showed a significant reduction in recurrent VTE, no difference in major bleeding and no difference in mortality.[44]

Overall, the authors of this meta-analysis determined that DOACs were more effective at preventing recurrent VTE regardless of site of thrombosis.[44] Differences in adherence did not contribute to these findings as on-treatment analysis found similar efficacy and safety. The authors confirmed significantly increased risk of GI bleeding in patients with GI cancers and increased major and non-major GU bleeding with DOACs. However, intracranial and fatal bleeding were similar between DOACs and LMWH.[44] When comparing incidental and symptomatic VTE, there were similar rates of recurrent VTE and major bleeding, further supporting the treatment of incidental CAT. Unfortunately, DOACs did not improve mortality when compared with LMWH, as treatment of VTE did not alter disease progression.[44]

A second meta-analysis evaluated DOACS during the on-treatment period and net clinical benefit based on a composite outcome of recurrent VTE and major bleeding.[45] Analysis of proximal DVT or PE versus any acute VTE had similar findings. The primary analysis included trials that only enrolled proximal DVT or PE.[36,37,39] DOACs had a non-significant decrease in recurrent VTE (RR 0.68, 95% CI 0.39–1.17) and non-significantly higher risk of major bleeding (RR 1.36, 95% CI 0.55–3.35) and CRNMB (RR 1.63, 95% CI 0.73–3.64). Surprisingly, the risk of fatal VTE was non-significantly higher with DOACs and the rate of non-fatal bleeding was non-significantly lower with DOACs in those with proximal DVT or PE. With respect to incidental VTE, there was no significant difference in recurrent VTE or major bleeding when comparing DOACs and LMWH.[45]

The authors also conducted a secondary analysis of patients with any acute VTE.[45] This showed the same findings as the primary analysis: a non-significant decrease in recurrent VTE and non-significant increases in major bleeding and CRNMB. During the on-treatment period, DOAC patients had significant reductions in recurrent VTE and no significant difference in major bleeding with both primary and secondary analyses. CRNMB was significantly elevated only in the any acute VTE group during the on-treatment period.

The authors of this second meta-analysis felt DOACs were an acceptable alternative to LMWH for the treatment of incidental and symptomatic CAT.[45] DOACs did show trends towards lower VTE recurrence and increased major bleeding, but neither of these were statistically significant. The net clinical benefit (a composite of recurrent VTE and major bleeding) also showed a non-significant decrease among those treated with DOACs. They suggest caution when DOACs are used in patients with a high risk of bleeding, especially those with luminal GI cancers. Increased major bleeding among those with GI cancers was seen in the Hokusai VTE Cancer and SELECT-D trials but not in the ADAM-VTE or Caravaggio trials.[36–39] The authors thought it was unclear whether this was due to different pharmacodynamics between the DOACs or if fewer patients with GI cancers were enrolled in the ADAM-VTE and Caravaggio studies.[38,39] Mortality rates were low in all studies, and VTE-related mortality rates were similar between DOACs and LMWH. Mortality related to major bleeding was lower for patients treated with DOACs.[45]

The most recent meta-analysis conducted by the authors of the CASTA DIVA trial incorporates their data with those from the previous four trials.[40] DOACs were associated with a significant reduction in recurrent VTE (RR 0.63, 95% CI 0.47–0.086) without a significant increase in major bleeding (RR 1.26, 95% CI 0.84–1.9). There was a significant increase in the composite of major bleeding and CRNMB (RR 1.48, 95% CI 1.18–1.85). The authors describe the similar results of this meta-analysis as providing additional support to the use of DOACs for the treatment of CAT, but also caution their use in patients with high bleeding risk.[40]

Duration of treatment

Major clinical guidelines recommend at least 3 months of therapeutic anticoagulation, with many suggesting up to 6 months of therapy

or longer (*Table 1*). Data on treatment beyond 6 months are limited.[2,7,20,33–35,40,46] The DALTECAN study investigated recurrent VTE and bleeding in extended dalteparin therapy for up to 12 months.[47] This study showed that recurrent VTE and major bleeding were highest during the first month of therapy but continued to decrease over the 12-month study period. Both major bleeding and recurrent VTE rated were lower in the latter 6 months of therapy compared with the first 6 months.[47] A similar study, TiCAT, was conducted to evaluate treatment of CAT with tinzaparin for up to 12 months.[48] Similarly to DALTECAN, the TiCAT study showed that treatment with LMWH in the latter 6 months was associated with reduced recurrent VTE incidence and clinically relevant bleeding (aggregate of major bleeding and CRNMB) compared with the first 6 months of treatment.[48]

The initial Hokusai VTE Cancer study reported outcomes for patients at 12 months but provided little information about outcomes during the first 6-month period. A *post-hoc* analysis compared the composite primary outcome (first recurrent VTE or major bleeding) between months 1–6 and months 6–12.[49] The primary outcome occurred at higher rates for both edoxaban and dalteparin (8.2% and 8.4%, respectively) during the first 6 months compared with the second 6 months (2.4% and 2.2%, respectively).[49] During the first 6 months, major bleeding was numerically higher in patients on edoxaban than in those on dalteparin (4.4% and 2.5%, respectively). In the second 6-month period, major bleeding was similar between edoxaban and dalteparin (1.7% and 1.1%, respectively).[49] Major GI bleeding occurred in 3.3% and 1.4% of patients treated with edoxaban during the first and second 6-month periods, respectively. Major GI bleeding rates were 0.6% and 0.4% in the first and second 6-month periods for dalteparin, respectively.[49] The authors note that during the first 6 months there were more patients with metastatic disease and worse performance status, which may account for the higher rates of primary outcome events during this time period. This *post-hoc* analysis showed that edoxaban was safe and effective when compared with dalteparin for extended treatment of CAT. It also confirmed what was seen in the prior LMWH trials – a reduction in both recurrent VTE and bleeding after the first 6 months of treatment.[49]

The SELECT-D:12m trial also sought to provide answers about extended therapy. Active cancer patients who completed the first 6 months of assigned therapy and had residual DVT or PE as their index event were eligible for a second randomization.[50] This trial was notably different from the initial SELECT-D study in that it compared rivaroxaban 20 mg daily to placebo for an additional 6 months. Dalteparin was not evaluated during this study. The primary outcome was VTE recurrence at 12 months. Unfortunately, due to low enrolment, the study was stopped. Only 58 of the 92 enrolled patients completed the 6 months of therapy.[50] Two patients in the rivaroxaban arm and six in the placebo arm developed recurrent VTE during the additional 6 months (HR 0.32, 95% CI 0.06–1.58). There was no major bleeding or CRNMB with placebo. Two patients (5%) in the rivaroxaban arm developed major bleeding, both of which were due to upper GI haemorrhages in lung cancer and colorectal cancer patients. This was similar to the major bleeding rate of 6% seen during the initial 6-month SELECT-D trial. Two patients (4%) on rivaroxaban also developed CRNMB.[50] This was much lower than the 13% CRNMB seen in the initial study. While the SELECT-D:12m trial did not have the power to show a significant difference in recurrent VTE, the data mimic major bleeding outcomes of the original study and may indicate improved CRNMB. The authors noted that patients in the second 6-month period had better performance status, early/locally advanced disease and had lower risk of VTE based on tumour type.[50] Individuals with active malignancy, those who are actively receiving antineoplastic therapy or those with metastatic disease remain at high risk for recurrent VTE. The American College of Chest Physicians, National Comprehensive Cancer Network, American Society of Clinical Oncology and American Society of Hematology all recommend extended anticoagulation with no scheduled stop date in these patients.[2,33–35,47,50] In these situations, it is recommended that patients remain on extended anticoagulation, but the decision to continue or discontinue treatment after 6 months of anticoagulation should be based on regular risk–benefit assessments that take into account efficacy of their antineoplastic therapies, VTE recurrence risk, bleeding risk and shared decision making.[7,20,34]

Table 2: Gastrointestinal and renal elimination of direct-acting oral anticoagulants

DOAC	Hepatic/biliary/intestinal elimination (%)	Renal elimination (%)
Apixaban	73	27
Dabigatran	20	80
Edoxaban	50	50
Rivaroxaban	67	33

DOAC = direct-acting oral anticoagulant.

Factors influencing anticoagulant choice

Choosing the optimal anticoagulant for CAT can be challenging. One important consideration is route of administration. Patients prefer oral administration over parenteral administration, but sometimes oral administration is not feasible – especially if individuals require nasogastric or gastrostomy tubes. Apixaban, rivaroxaban and edoxaban can be crushed and administered through gastric tubes.[51–53] Delivery of any of these three DOACs beyond the stomach may result in decreased efficacy. VKAs involve a known higher burden of treatment due to restrictions in dietary variation, frequent laboratory monitoring and dosage changes to maintain therapeutic ranges.

DOACs are often prescribed as first-line therapy for non-cancer-associated VTE, but some clinical guidelines still recommended LMWH as first line for initiation, maintenance and long-term therapy in CAT due to concerns with DOACs and renal or hepatic dysfunction, drug–drug interactions, body weight limitations and absorption concerns.[7,20] Rates of renal and hepatic elimination for each DOAC are shown in *Table 2*. Unfortunately, decreased adherence and early discontinuation of LMWH has been documented in several studies, likely due to cost and subcutaneous route of administration.[11] More recent guidelines take into account that DOACs are orally administered, have fixed dosing regimens, do not need frequent laboratory monitoring, and have shown to be at least as efficacious as warfarin and LMWH for preventing recurrent VTE.[2,4]

In situations of upper GI tract resections, there may be issues with drug absorption and, therefore, potential decreased efficacy. The bioavailability of 15 mg and 20 mg doses of rivaroxaban are dependent on administration with meals and passage through the stomach. Peak concentration and bioavailability increase when taken with food, but direct administration into the small intestines would result in a 56% reduction in concentration.[54,55] For individuals who have undergone total or partial gastrectomy and bariatric surgeries that reduce stomach size or caloric intake, rivaroxaban may not be absorbed effectively enough to treat VTE. Apixaban is not dependent on administration with food, but the majority of its absorption occurs in the small bowel, with some absorption occurring in the stomach and less in the ascending colon.[54,55] Absorption may be a concern in patients with surgeries that bypass or

resect parts of the small intestine. The absorption of edoxaban is highly dependent on an acidic environment that increases its solubility before absorption in the small intestine. Patients with gastrectomy or small-bowel resections may be at risk for decreased drug absorption and impaired efficacy.[55]

Future treatment considerations

As more information becomes available supporting the use of anticoagulation for extended treatment as secondary prophylaxis in CAT, the question of optimal dosage arises. The aforementioned DALTECAN and TiCAT studies – which showed reductions in both recurrent VTE and bleeding during extended therapy – did not change their dosing regimens for months 1–6 and months 7–12.[47,48] Of the limited studies with DOACs, Hokusai VTE Cancer and SELECT-D:12m also continued the same doses throughout the 12-month study periods.[36,50] Both studies showed a reduction in recurrent VTE and bleeding over the 12-month periods in each drug arm. The authors of both studies postulate that patients who continued past the initial 6 months were fitter with better performance status and less advanced disease, resulting in decreased recurrent VTE, bleeding and mortality.[36,50]

A recent study and two ongoing trials aim to answer questions about the efficacy and safety of reduced-dose DOACs for secondary prophylaxis in CAT. A multicentre, single-arm trial in Norway assessed recurrent VTE, major bleeding and CRNMB in patients treated for 6 months with apixaban 5 mg twice daily followed by 2.5 mg twice daily for an additional 30 months.[56] The groups were similar in proportions of gender, metastatic disease and cancer types, but the low-dose cohort was slightly older. Patients receiving full-dose apixaban during the first 6 months had a 4% (95% CI 2.1–6.9) recurrent VTE rate compared with 7.1% (95% CI 4.0–11.7) in the low-dose extended treatment group, which mostly occurred in months 7–12.[56] Major bleeding and CRNMB occurred in 5.4% and 8.7% of the full-dose cohort during the first 6 months, respectively. Low-dose cohort experienced 3.1% major bleeding and 8.2% CRNMB rates over the next 30 months. Six of the 16 major bleeds during the first 6 months occurred in GI cancers, of which four were unresected and two were resected tumours. During the 30-month secondary prophylaxis period, there were six major bleeding events, two occurring in patients with GI cancers. A *post-hoc* composite endpoint of recurrent VTE and major bleeding showed the highest incidence in the first 9 months of treatment, especially in the first month.[56] It is unclear whether the increased risk of VTE with low-dose apixaban is truly offset by the reduction in bleeding. The lack of randomization and control group, as well as being conducted in a single country, are all limits to this trial that prevent its results from being applied to the general CAT population.

The ongoing EVE trial and API-CAT study aim to answer the questions that remain about reduced-dose DOACs for the extended treatment of CAT.[57,58] The EVE trial is a multicentre, randomized, double-blind trial in the USA and Canada that seeks to compare bleeding rates between full-dose (5 mg twice daily) and low-dose (2.5 mg twice daily) apixaban during 12 months of extended treatment.[57] Inclusion criteria are similar to the ADAM-VTE study: patients with active cancer with upper/lower extremity DVT, cerebral sinus thrombosis, splanchnic thrombosis or PE who have completed at least 6 months of therapeutic anticoagulation. The primary outcome is a composite of major bleeding, fatal bleeding and CRNMB. The secondary outcome is a composite of recurrent DVT/PE, fatal PE or arterial thromboembolism (myocardial infarction, stroke, transient ischaemic attack or peripheral arterial embolism).[57]

The API-CAT study is an international prospective, randomized, double-dummy, non-inferiority trial to compare extended therapy with full-dose (5 mg twice daily) or low-dose (2.5 mg twice daily) apixaban over 12 months.[58] It is currently enrolling patients with active cancer and symptomatic or incidental PE, inferior vena cava, iliac or proximal DVT who have completed at least 6 months of anticoagulant therapy with a VKA, DOAC or LMWH.[58] The primary efficacy outcome is a composite of recurrent symptomatic or incidental VTE or death due to PE during the 12-month treatment period. Secondary outcomes include a composite of major bleeding or CRNMB, VTE-related death and all-cause death.[58] The investigating team for both the EVE trial and the API-CAT study hope to show that extended treatment with low-dose apixaban is as effective as the full dose for secondary CAT prophylaxis, with lower bleeding rates.

Conclusions

CAT has a significant impact on patient mortality and also affects quality of life. Treatment paradigms have changed, and DOACs are now considered as first-line agents in properly selected patients. DOACs have shown themselves to be at least as effective in preventing recurrent VTE in patients with cancer and symptomatic and incidental VTE. For those with luminal GI or GU cancers, patients should be made aware of the increased risk of bleeding. Treatment guidelines for CAT recommend at least 6 months of therapy, with some recommending a longer time course for secondary prevention, which in some cases may be indefinite. Ongoing studies examining the efficacy and safety of low-dose DOACs may reduce concerns about their use in populations at high risk of bleeding. In patients who cannot tolerate oral intake, with certain feeding tubes or after certain gastric surgeries, DOACs become less feasible due to absorption concerns. In these situations, LMWH is still an effective choice for the treatment of CAT. The use of DOACs can remove the pain or anxiety that comes with frequent LMWH injections and improve quality of life. ❑

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Glossary

ADAM VTE:	Apixaban or Dalteparin in Reducing Blood Clots in Patients With Cancer Related Venous Thromboembolism (ClinicalTrials.gov Identifier: NCT02585713)
API-CAT:	API-CAT STUDY for APIxaban Cancer Associated Thrombosis (API-CAT) (ClinicalTrials.gov Identifier: NCT03692065)
Caravaggio:	Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer (CARAVAGGIO) (ClinicalTrials.gov Identifier: NCT03045406)
CASTA DIVA:	Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban (CASTA-DIVA) (ClinicalTrials.gov identifier: NCT02746185)
CATCH:	Long-Term Innohep® Treatment Versus a Vitamin K Antagonist (Warfarin) for the Treatment of Venous Thromboembolism (VTE) in Cancer (ClinicalTrials.gov identifier: NCT01130025)
CLOT:	Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer
DALTECAN:	Evaluation of Dalteparin for Long-term (One Year) Treatment of Blood Clots in Subjects With Cancer (ClinicalTrials.gov Identifier: NCT00942968)
EVE:	Apixaban in Preventing Secondary Cancer Related Venous Thrombosis in Cancer Patients Who Have Completed Anticoagulation Therapy (ClinicalTrials.gov Identifier: NCT03080883)
Hokusai VTE Cancer:	Cancer Venous Thromboembolism (VTE) (ClinicalTrials.gov Identifier: NCT02073682)
LITE:	Trial of the Effect of Low-Molecular-Weight Heparin (LMWH) Versus Warfarin on Mortality in the Long-Term Treatment of Proximal Deep Vein Thrombosis (DVT) (Main LITE Study) (ClinicalTrials.gov identifier: NCT00203580)
ONCENOX:	Secondary Prevention of Venous Thromboembolic Events in Patients With Active Cancer: Enoxaparin Alone Versus Initial Enoxaparin Followed by Warfarin for a 180-Day Period
REITE:	Registro Informatizado Enfermedad Trombo Embólica (The Computerized Registry of Patients with Venous Thromboembolism)
SELECT-D:	Comparison of an Oral Factor Xa Inhibitor with Low Molecular Weight Heparin in Patients with Cancer with Venous Thromboembolism: Results of a Randomized Trial (SELECT-D) (ISRCTN number: ISRCTN86712308)
SELECT-D:12m:	Treatment of Cancer-associated Venous Thromboembolism: 12-month Outcomes of the Placebo versus Rivaroxaban Randomization of the SELECT-D Trial (SELECT-D: 12m)
TiCAT:	Tinzaparin in Cancer Associated Thrombosis Beyond 6 Months: TiCAT study