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Anticoagulation for cancer-associated thrombosis

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Abbreviations used in this review
BMI = body mass index
CAT = cancer-associated thrombosis
CI = confidence interval
DOAC = direct oral anticoagulant
DVT = deep vein thrombosis
GI = gastrointestinal
HR = hazard ratio
INR = international normalised ratio
IU = international unit
LMWH = low-molecular-weight heparin
PE = pulmonary embolism
PIC = peripherally inserted central catheter
SC = subcutaneous
VEGF = vascular endothelial growth factor
VKA = vitamin K antagonists
VTE = venous thromboembolism

This review discusses the treatment of cancer-associated venous thromboembolism (VTE) and the prevention of recurrent cancer-associated VTE. Patients with cancer are particularly susceptible to developing VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), and exhibit an elevated risk of recurrent VTE despite anticoagulant therapy.[1] Furthermore, cancer patients tend to have a higher risk of bleeding, making the management of VTE in this population particularly challenging.[1] For the past decade, low-molecular-weight heparins (LMWHs) have been the standard of care for cancer-associated VTE, however, only 50% of patients manage to adhere to long-term treatment.[1,2]

Recent data on direct oral anticoagulants (DOACs) including the factor Xa inhibitors rivaroxaban [Xarelto®], apixaban [Eliquis®]* and edoxaban [Savaysa®; Lixiana®]**, which are well established as first-choice treatments of VTE in non-cancer patients, have demonstrated efficacy and safety in selected cancer patients with VTE.[3,4] Oral factor Xa inhibitors may offer a more convenient and less invasive treatment option than LMWH for cancer-associated VTE, but they may not be suitable for use in all cancer patients.[5] Rivaroxaban is the only fully funded oral factor Xa inhibitor available in New Zealand and it is funded by Pharmac without restriction for people who require an oral anticoagulant.[6] This publication has been commissioned by Bayer. The production of the content is entirely independent but has been reviewed by Bayer prior to publication.

*apixaban is not funded in NZ

**edoxaban is not registered for use in NZ

Cancer-associated thrombosis (CAT)

VTE is a potentially fatal, chronic and recurrent disease and is the second most prevalent cause of death from cancer, second only to the progression of cancer itself.[7,8] The relationship between thrombosis and cancer is long established and it is well recognised that VTE is associated with significant morbidity and mortality in patients with malignancy.[1,9,10] Individuals with cancer-associated thrombosis (CAT) experience a reduced quality of life, interruptions and delays in anticancer therapies, and ultimately an estimated 6-fold decrease in survival rates compared to individuals with cancer without thrombosis.[11,12] CAT can be contrasted to VTE in the non-cancer setting in terms of pathophysiological mechanism and risk factors, as well as specific treatment issues.[8]

In general terms, patients who recover from a VTE episode may experience long-term morbidities including pulmonary hypertension and post-thrombotic syndrome manifesting as swelling, pain, oedema, fibrosis, venous ectasia and skin induration (estimated to occur in 23-60% of patients within 2 years of a symptomatic DVT episode).[7,13] Furthermore, a diagnosis of VTE impacts on future surgery, oestrogen use, pregnancy, life insurance and sometimes long-haul travel.[7]

It is estimated that cancer patients are at a 4- to 7-fold higher risk of developing VTE than non-cancer patients, with an annual incidence of VTE in patients with cancer estimated to be 0.5% versus 0.1% in the general population.[1,8] Active cancer accounts for approximately 20% of the overall incidence of VTE.[8] Once an index VTE has occurred, patients with malignancy have a 3-fold higher risk of VTE recurrence, even when receiving anticoagulation, and a 2-fold higher risk of major bleeding than non-cancer patients.[14] The incidence of CAT varies with different malignancies: upper gastrointestinal tumours, pancreatic cancer and ovarian cancer have particularly high rates.[15]

The incidence of CAT has increased over recent decades, partly due to a greater awareness of the association between cancer and VTE, more elderly patients undergoing more cancer treatments, and improved imaging techniques leading to increased detection of incidental VTE.[10,16] As many as 50% of PEs in cancer patients are diagnosed on scans done for other purposes.[17] Furthermore, VTE may be the first manifestation of cancer, with up to 10% of patients presenting with unprovoked VTE being diagnosed with cancer within 1 year.[7]

Why are cancer patients at greater risk of VTE?

Patients with cancer are generally in a hypercoagulable or prothrombotic state, with abnormalities in each component of Virchow's triad (stasis of blood flow, endothelial injury, hypercoagulability) contributing to thrombosis.[9] It is clear that several mechanisms (both direct and indirect) can promote a hypercoagulable state and that the process of thrombotic generation in patients with cancer is distinct from that in non-cancer patients.[8,9] Among the key players is a protein called tissue factor, found in the subendothelial tissues for the initiation of normal haemostasis, but which is critical in the process of VTE formation when produced by cancer cells.[8,18] This protein activates the extrinsic coagulation pathway resulting in the activation of factor X and consequently fibrin synthesis.[8]

Risk factors for CAT

Substantial variations in VTE risk are evident amongst individuals with malignancy and many factors including cancer type, stage, tumour-derived factors, genetics, the presence of metastases, cancer treatment (surgical or medical), the use of central venous catheters, and immobility all affect the risk of CAT (**Figure 1**).[8,11,19,20] The presence of metastases increases the risk of CAT multi-fold compared to localised disease.[19]

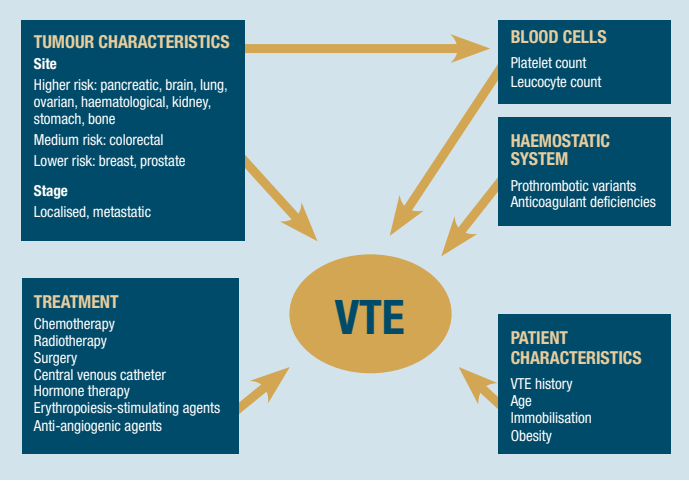

Figure 1. Risk factors for thrombosis in patients with cancer. (Adapted from Hisada et al. 2015 and Horsted et al. 2012)[11,20]

Cancer treatment itself contributes to the risk of VTE, with cytotoxic chemotherapy having a multifactorial contribution to the risk of thrombosis via vascular injury through apoptosis and von Willebrand factor elevations, 5-fluorouracil driving thrombin formation in combination with depleted protein C activity, and VEGF inhibitors, immunomodulatory agents and small molecule inhibitors `priming' the endothelium to be more susceptible to injury.[21] The impact of cancer-related surgery is also significant in CAT with a 2-fold increased risk of VTE in cancer patients requiring surgery when compared with non-cancer patients undergoing comparable surgery; the increased risk of VTE varies substantially with the type of surgery (e.g. 13.7% risk with oesophageal surgery vs 1.7% with prostatectomy).[19]

The American Society of Clinical Oncology (ASCO) recommends that oncologists and members of the oncology team educate patients regarding VTE, particularly in settings that increase risk, such as major surgery, hospitalisation, and while receiving systemic antineoplastic therapy.[22]

Assessing the risk of CAT

ASCO guidelines recommend that patients with cancer should be assessed for VTE risk initially and periodically thereafter, particularly when starting systemic antineoplastic therapy or at the time of hospitalisation.[22] Prophylaxis should be used for major cancer surgery, and should be continued out to 4 weeks for major abdominal or pelvic procedures in patients with other VTE risk factors[#].[22] In the outpatient chemotherapy setting, use of the Khorana score is recommended (**Table 1**); the Khorana score is a VTE risk assessment model specifically for ambulatory patients with cancer that takes into account cancer site, the use of erythropoiesis-stimulating agents, platelet count, leucocyte count and BMI, and stratifies patients into low (score 0), intermediate (score 1-2) and high (score ≥3) risk of VTE.[22,23] With regard to thromboprophylaxis, the ASCO guidelines state that high-risk outpatients with cancer (Khorana score of ≥2 prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis provided there are no significant risk factors for bleeding and no drug interactions, and that consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting[##].[22]

[#]In NZ only LMWH is indicated for VTE prophylaxis in high-risk surgery and DOACs are not approved for such use. [##]While ASCO recommends offering thromboprophylaxis to high-risk patients in the cancer setting, in NZ, neither LMWH nor DOACs are indicated for this use.

Table 1. Khorana predictive model for chemotherapy-associated VTE risk[23]

Patient characteristic	Risk score
Cancer site	
• Very high risk (stomach, pancreas)	2
• High risk (lung, gynaecological, bladder, testicular, lymphoma)	1
Prechemotherapy platelet count ≥350 × 10^9/L	1
Haemoglobin level <100 g/L, or red-cell growth factor use	1
Prechemotherapy leucocyte count >11 × 10^9/L	1
BMI ≥35 kg/m^2	1

Anticoagulant therapy for CAT

The efficacy and safety of anticoagulation are not equivalent in cancer and non-cancer patients, with cancer patients more likely to experience a recurrence of VTE even while on anticoagulants and being more prone to the most severe adverse event of anticoagulant therapy, bleeding.[8] International guidelines emphasise the importance of individualised treatment regimens and shared decision-making in the management of patients requiring anticoagulation for CAT.[24]

When choosing which anticoagulant to use, clinicians must take a detailed clinical history, ascertaining the cancer type, status, treatment, concomitant medications and bleeding risk.[25] Patients should be informed of the potential reduction in recurrence of VTE but the higher risk of bleeding with some agents, and patient preferences and values should be incorporated into the management plan.[24] Because the course of treatment for CAT is often prolonged, healthcare professionals need to be attentive to patient compliance and educate patients about the rationale behind anticoagulation therapy and optimal administration techniques.[26]

Anticoagulants available in New Zealand for the treatment of acute VTE are detailed in **Table 2**.[7]

Table 2. Anticoagulant options available in New Zealand and Australia for the treatment of acute VTE[7]

Rivaroxaban†
Apixaban* **
Dabigatran‡
Warfarin
LMWH§

† Requires CrCl ≥15 mL/min. * Requires CrCl ≥25 mL/min. ** Apixaban is not funded in New Zealand. ‡ Requires CrCl ≥30 mL/min. § If LMWH is required for a patient with CrCl ≤30 mL/min, seek expert advice. Twice-daily dosing of dalteparin and enoxaparin may be preferred for patients at high risk of bleeding, such as patients who are older, are at extremes of weight (e.g. ≥150 kg) or who have a malignancy.

VKAs vs LMWHs

In 2003, the CLOT trial comparing the LMWH*** dalteparin [Fragmin][a] with the vitamin K antagonists (VKAs) warfarin [Marevan, Coumadin] or acenocoumarol [Sintrom] for the prevention of recurrent VTE over 6 months in patients with cancer found that subcutaneous (SC) dalteparin was significantly more effective than oral warfarin or acenocoumarol in reducing the risk of recurrent thromboembolism (HR 0.48; 95% CI 0.30-0.77, p = 0.002) without increasing the risk of major bleeding (6% vs 4%; p = 0.27).[27] As a result of these findings and the difficulties associated with long-term adherence to VKAs, especially in patients with malignancy, including drug interactions, vomiting, kidney and liver dysfunction, chemotherapy-induced thrombocytopenia and the need for intensive INR monitoring, narrow therapeutic indices, interactions with some foods and the often frequent need for dose adjustments, LMWHs (enoxaparin sodium [Clexane, Clexane Forte®, Crusia-AFT[a]; Crusia-AFT Forte[a]], dalteparin [Fragmin®[a]]) became the gold standard of care for CAT.[1,3,8,28] The long-term (6 months) use of LMWHs in CAT was subsequently supported by a number of other studies.[8]

Despite guideline recommendations for its use in CAT, adherence to LMWH is often not easily achieved, with patients reporting issues such as local pain due to the administration method, and bleeding.[8,26,29] In a study involving 372 patients with CAT treated with LMWH, 51% discontinued treatment within 6 months, with 21% stopping treatment due to side-effects including unacceptable pain at the injection site (8.9%), large local injection site haematomas (7.3%), allergic reactions (4%), and heparin-induced thrombocytopenia (0.81%); major bleeding occurred in 1.1% of patients.[29]

*** LMWH is the only therapy indicated for the primary prophylaxis of VTE in cancer patients in NZ
[a] Crusia-AFT, Crusia-AFT Forte and dalteparin [Fragmin®] are not funded in NZ

DOACs

Limitations of traditional VTE therapies have led to the development of direct oral anticoagulants (DOACs) such as the factor Xa inhibitors rivaroxaban [Xarelto®], apixaban [Eliquis®] and edoxaban [Savaysa®; Lixiana®][b], and the direct thrombin inhibitor dabigatran [Pradaxa®][c] which in addition to their favourable efficacy and safety profiles have more convenient administration regimens.[3,28] Introduced for the treatment of VTE just over a decade ago, DOACs are given in fixed doses, unlike warfarin which requires adjustment and laboratory monitoring.[25] While DOACs are similar to VKAs in efficacy, they are much more convenient to use.[25]

[b] edoxaban is not registered for use in NZ
[c] parenteral anticoagulant required before dabigatran administration

A recent meta-analysis of 4 key oral factor Xa inhibitor trials (Hokusai VTE Cancer study; SELECT-D; CARAVAGGIO; and the ADAM VTE trial – discussed below) enrolling a total of 2894 cancer patients treated with rivaroxaban, edoxaban, apixaban or the LMWH dalteparin for acute VTE revealed that DOACs were associated with a 38% reduced risk of VTE recurrence at 6 months (RR 0.62; 95% CI 0.43-0.91).[3]

The oral factor Xa inhibitors do however carry a risk of major bleeding in patients with CAT and this appears to be higher in patients with certain types of cancer.[5] Several trials (discussed below) have compared the different oral factor Xa inhibitors for the treatment of CAT, but have given somewhat conflicting results, likely due to their patient selection (cancer type and prognosis) and primary outcome.[5] While the findings of the CARAVAGGIO trial (apixaban vs dalteparin; discussed below) are suggestive that apixaban may be safer than rivaroxaban or edoxaban with regard to major bleeding, it should be noted that the CARAVAGGIO trial excluded patients with primary and metastatic brain lesions and included few patients with haematological cancers and cancers of the upper gastrointestinal tract.[5] Furthermore, the ADAM VTE trial which also demonstrated low rates of major bleeding with apixaban and dalteparin (also discussed below) was a small study with a low mortality rate possibly also indicating patient selection.[30]

The SELECT-D study (rivaroxaban vs dalteparin) was a pilot study for feasibility, although of a large size for this purpose.[31] Oesophageal cancer was excluded after the first safety analysis due to bleeding concerns on rivaroxaban.[31]

Due to the heterogeneity of the trials comparing DOACs, it is inappropriate to conclude that one DOAC is better than the other.[25] The impact of patient selection on major bleeding rates may be evidenced by a single-institution cohort study that revealed that limiting rivaroxaban use to cancer patients without active gastrointestinal or urinary tract lesions, with a dose reduction in elderly patients, resulted in a 6-month major bleeding rate of only 2.2%.[4]

Dabigatran has not been compared to LMWH in the cancer setting. In the RECOVER VTE studies, including a small cancer population, dabigatran was not different to warfarin, the comparator, which itself is generally considered inferior in the active cancer setting due to higher risks of recurrent VTE.[32]

Advantages of DOACs[6,24]

- Oral administration
- Routine coagulation monitoring not required
- Lower recurrent VTE rates
- No LMWH lead-in period required for rivaroxaban and apixaban
- Rivaroxaban does not require dose adjustments for age, sex, bodyweight or ethnicity.

Disadvantages of DOACs[6,22,24]

- Increased bleeding risk
- Drug-drug interactions*
- LMWH lead-in period required for dabigatran and edoxaban
- Nausea and vomiting in cancer patients may impact adherence to DOACs
- Rivaroxaban should be taken with food.

*avoiding the concomitant use of drugs that are potent inhibitors or inducers of P-glycoprotein or cytochrome P450 3A4 is necessary[24]

Key DOAC trials in CAT

Edoxaban vs dalteparin: The Hokusai VTE Cancer study was the first to compare the DOAC (edoxaban) with the LMWH (dalteparin) in cancer patients and demonstrated that once-daily oral edoxaban (median duration 211 days) was non-inferior to once-daily SC dalteparin (median duration 184 days) for the combined outcome of recurrent thrombosis and major bleeding (HR 0.97; 95% CI 0.70-1.36, p = 0.006 for non-inferiority).[33] In this trial, major bleeding (secondary endpoint) was experienced by significantly more edoxaban recipients than dalteparin recipients (6.9% vs 4.0%, HR 1.77 [95% CI 1.03-3.04], p = 0.04); this increase in bleeding was mainly due to upper gastrointestinal bleeding in patients with upper gastrointestinal cancers.[33]

Rivaroxaban vs enoxaparin + warfarin/acenocoumarol

The pivotal randomised, open-label EINSTEIN-DVT and EINSTEIN-PE studies compared the efficacy and safety of oral rivaroxaban 15 mg twice-daily for 21 days followed by 20 mg once-daily with that of SC enoxaparin 1.0 mg/kg twice-daily (median duration 8 days) with and followed by an INR-titrated vitamin K antagonist (oral warfarin or acenocoumarol) for 3, 6 or 12 months in over 8000 patients with acute symptomatic DVT or PE.[34,35] Both studies found that rivaroxaban was non-inferior to standard therapy for the primary outcome of symptomatic recurrent VTE.[34,35]

While the EINSTEIN studies weren't specifically designed to assess the efficacy/safety of rivaroxaban in patients with active cancer, and the comparator arm did not use standard-of-care treatment for this group, a pooled subgroup analysis in cancer patients revealed similar rates of recurrent VTE in rivaroxaban (n = 354) and enoxaparin + warfarin/acenocoumarol treatment groups (5% vs 7%; HR 0.67; 95% CI 0.35-1.30; n = 301).[36] There were fewer major bleeding episodes in patients with active cancer receiving rivaroxaban than those receiving enoxaparin + warfarin/acenocoumarol (2% vs 5%; HR 0.42; 95% CI 0.18-0.99), but rates of clinically relevant bleeding were similar between the two treatment groups (14% vs 16%; HR 0.80; 95% CI 0.54-1.20).[36]

Rivaroxaban vs dalteparin: The multicentre, randomised, open-label, pilot SELECT-D (Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism) trial, compared rivaroxaban (15 mg orally twice daily for 3 weeks, then 20 mg once daily for 6 months; n = 203) with dalteparin (200 IU/kg SC daily during month 1, then 150 IU/kg daily for months 2-6; n = 203) in patients with active cancer and VTE.[31] Rivaroxaban was associated with a lower risk of cumulative VTE recurrence at 6 months (primary outcome) compared with dalteparin (4.0% vs 11.0%; HR 0.43; 95% CI 0.19-0.99).[31] However, for the secondary outcome of clinically relevant non-major bleeding (CRNMB), rivaroxaban was associated with a significantly higher rate than dalteparin at 6 months; 13% vs 4% (HR 3.76; 95% CI 1.63-8.69).[31] For the secondary outcome of major bleeding at 6 months the rate was 6% with rivaroxaban and 4% with dalteparin (HR 1.83: 95% CI 0.68-4.96).[31]Most major bleeding events were gastrointestinal and there were no CNS bleeds, while CRNMBs were mostly gastrointestinal or urologic.[31]

Apixaban vs dalteparin: Contributing to the evidence for the use of DOACs in patients with CAT, is the recently published multinational, randomised, investigator-initiated, open-label, non-inferiority CARAVAGGIO trial, patients with cancer and VTE received either oral apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily; n = 576) or SC dalteparin (200 IU/kg once daily for 1 month followed by 150 IU/kg daily; n = 579) for 6 months.[37] The primary outcome, objectively confirmed recurrent VTE during treatment occurred in 5.6% of apixaban versus 7.9% of dalteparin recipients (HR 0.63; 95% CI 0.37-1.07; p < 0.001 for non-inferiority; p = 0.09 for superiority).[37] Major bleeding (principle safety outcome) occurred at similar rates in apixaban and dalteparin recipients (3.8% vs 4.0%; HR 0.82; 95% CI 0.40-1.69; p = 0.60); the rates of major gastrointestinal bleeding were also similar between the two groups (1.9% vs 1.7%, HR 1.05; 95% CI 0.44-2.50).[37]

The CARAVAGGIO trial authors report that the similar rates of major bleeding observed between apixaban and dalteparin are in contrast to that previously seen with other DOACs (rivaroxaban [SELECT-D trial]; edoxaban [Hokusai VTE Cancer study]), where DOACs exhibited significantly higher rates of major bleeding when compared with dalteparin.[31,33,37]

The multicentre, randomised, open-label ADAM VTE trial comparing apixaban to dalteparin in CAT found similar findings to the CARAVAGGIO trial, with major bleeding (primary outcome) occurring in a statistically similar number of patients during approximately 6 months of treatment: 0% of 145 patients receiving apixaban and 1.4% of 142 dalteparin recipients (p = 0.138).[30]

Apixaban vs rivaroxaban/enoxaparin: A prospective study of consecutive patients with acute CAT treated with apixaban (n = 224), rivaroxaban (n = 163) or enoxaparin (n = 363) at the Mayo Thrombophilia Clinic compared the effectiveness and safety of these treatments.[38] The VTE recurrence rates did not differ significantly between treatment groups: apixaban 7.74 per 100 person-years versus rivaroxaban 3.82 per 100 person-years (HR 1.31; 95% CI 0.51-3.36); apixaban versus enoxaparin 5.56 per 100 person-years (HR 1.14; 95% CI 0.54-2.42); rivaroxaban vs enoxaparin (HR 0.85; 95% CI 0.36-2.06).[38] The rates of major bleeding were also similar between the three treatment groups: apixaban 7.73 per 100 person-years versus rivaroxaban 6.74 per 100 person-years (HR 0.73; 95% CI 0.32-1.66); enoxaparin 6.99 per 100 person-years versus apixaban (HR 0.89; 95% CI 0.43-1.84); enoxaparin vs rivaroxaban (HR 1.23; 95% CI 0.61-2.50).[38]

Real-world evidence (rivaroxaban, LMWH, warfarin): A retrospective longitudinal cohort study compared the risk of VTE recurrence and major bleeding with rivaroxaban (n = 707), LMWH (n = 660) or warfarin (n = 1061) in patients with CAT.[39] VTE recurrence rates at 6 months did not significantly differ between rivaroxaban and LMWH recipients (13.2% vs 17.1%; p = 0.060), but the difference was significant at 12 months, with rivaroxaban recipients exhibiting a 28% decreased risk of VTE recurrence (16.5% vs 22.2%; HR 0.72; 95% CI 0.52-0.95; p = 0.024). VTE recurrence rates at both 6 (13.2% vs 17.5%; p = 0.014) and 12 (15.7% vs 19.9%; p = 0.017) months were also significantly lower for rivaroxaban than warfarin recipients, with rivaroxaban associated with a 26% decreased risk of VTE recurrence; HR 0.74 (95% CI 0.56-0.96), p = 0.028.[39] The VTE recurrence rate was similar between warfarin and LMWH recipients.[39] The rates of major bleeding were similar between treatments at 6 months; rivaroxaban vs LMWH (8.2% vs 8.3%), rivaroxaban vs warfarin (9.0% vs 8.7%), LMWH vs warfarin (8.5% vs 8.6%).[39] In each treatment group, the majority of major bleeding events were gastrointestinal.[39]

Expert commentary on key DOAC trials

There are common themes for the Xa inhibitor trials in CAT: overall these medicines are effective at preventing recurrent VTE but bleeding risk requires careful assessment. Apixaban is appealing with lower bleeding rates in the CAT trial (CARAVAGGIO) as well as atrial fibrillation anticoagulation studies, but trial design differences do mean that the studies of the individual Xa inhibitors cannot be directly compared, and it is difficult to exclude selection bias in observational cohort studies. LMWH is preferred where patients have gastrointestinal tumours or genitourinary tumours in situ and there is no clinical trial evidence to support the use of dabigatran for CAT specifically. No doubt more observational evidence will augment the available real-world data over coming years.

Guideline recommendations for CAT

The following are key points from international guidelines for the treatment of CAT (for full guideline recommendations please see the individual guidelines).

ISTH (International Society of Thrombosis and Hemostasis) guidelines recommend:[24]

- Individualised treatment regimens after shared decision-making with patients, acknowledging a potential reduction in VTE recurrence risk but the higher rates of bleeding with specific DOACs
- The use of specific DOACs (e.g., rivaroxaban and edoxaban) for cancer patients with acute diagnosis of VTE, low risk of bleeding and no drug-drug interactions with current systemic therapy
- The use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding (including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, oesophagitis, or colitis). Rivaroxaban and edoxaban are acceptable alternatives if there are no drug-drug interactions with current systemic therapy.

ASCO (American Society of Clinical Oncology) clinical practice guidelines recommend:[22]

- Initial anticoagulation with LMWH, unfractionated heparin, fondaparinux#, or rivaroxaban
- For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred. VKAs are inferior but may be used if LMWH or DOACs are not accessible
- Drug-drug interactions should be checked prior to using a DOAC
- Caution with DOACs is warranted in settings with high-risk mucosal bleeding. There is an increased risk of major bleeding with DOACs, particularly observed in gastrointestinal and potentially genitourinary malignancies
- Anticoagulation with LMWH, DOACs or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.

#not routinely used in NZ for patients with VTE

THANZ (Thrombosis and Haemostasis Society of Australia and New Zealand) guidelines recommend:[7]

- Proximal DVT or PE that is recurrent (2 or more) and provoked by active cancer should receive extended anticoagulation.

Expert's concluding remarks

Working in a tertiary hospital Thrombosis Unit, CAT is a very common problem. Around one-third of our VTE referrals are being managed for active cancer. Many VTE events are now diagnosed on routine staging but are treated the same way due to clear evidence that these events have similar risks of VTE recurrence. Line-associated thrombosis with PIC lines or port-a-caths is also common: it is useful to note that the line can be left in situ with anticoagulation treatment if needed.

Bleeding and VTE recurrence are more problematic in the cancer setting. In New Zealand, our therapy of choice has been LMWH, most often enoxaparin, for many years. For patients with malignancies of the gastrointestinal or genitourinary tracts, with tumours in situ, we still use enoxaparin as preferred therapy on a tapering dose schedule. There are no DOAC trial data for treatment of line-associated thrombosis so we tend to start with enoxaparin in this setting also. In other cancer patients with VTE we are however transitioning to the use of rivaroxaban (which is the PHARMAC funded Xa inhibitor currently available in NZ), sometimes after initial enoxaparin.

It is important that bleeding risk factors are regularly assessed, for example thrombocytopenia with chemotherapy or recent surgery, in addition to the aforementioned issue of tumour location. Prevention of VTE is of course ideal and enoxaparin is generally used for surgical prophylaxis. The ASCO guidelines have introduced the concept of ambulatory cancer outpatient prophylaxis for selected high thrombosis risk patients although rivaroxaban is not registered specifically yet for this indication, and PHARMAC special authority criteria for enoxaparin only include the treatment of CAT at this point.

There has been significant progress in high quality randomised research over the last few years for the treatment and prevention of CAT.

Contraindications to therapeutic anticoagulant use in CAT

Table 3. Contraindications to therapeutic anticoagulant therapy in patients with cancer[22]

Absolute contraindications*
Non-DOACs and DOACs
Active major, serious, or potentially life-threatening bleeding not reversible with medical or surgical intervention, including but not limited to any active bleeding in a critical site (eg, intracranial, pericardial, retroperitoneal, intraocular, intra-articular, intraspinal)
Severe, uncontrolled malignant hypertension
Severe, uncompensated coagulopathy (eg, liver failure)
Severe platelet dysfunction or inherited bleeding disorder
Persistent, severe thrombocytopenia (<20,000/μL)
High-risk invasive procedure in a critical site, including but not limited to lumbar puncture, spinal anesthesia, epidural catheter placement
DOAC specific
Concurrent use of potent P-glycoprotein or CYP3A4 inhibitors or inducers
Relative contraindications†
Non-DOACs and DOACs
Intracranial or spinal lesion at high risk for bleeding‡§
Active GI ulceration at high risk of bleeding‡§
Active but non–life-threatening bleeding (eg, trace haematuria)‡§
Intracranial or CNS bleeding within past 4 weeks‡§
Recent high-risk surgery or bleeding event‡§
Persistent thrombocytopenia (<50,000/μL)‡§
Patients for whom anticoagulation is of uncertain benefit
Patient receiving end-of-life/hospice care
Very limited life expectancy with no palliative or symptom reduction benefit
Asymptomatic thrombosis with concomitant high risk of serious bleeding
Patient characteristics and values
Preference or refusal
Nonadherence to dosing schedule, follow-up, or monitoring

*Absolute contraindications are situations in which anticoagulation should not be given because the risk of harm associated with bleeding is very likely to exceed the potential benefit from anticoagulation. †Relative contraindications are situations in which anticoagulation may be given if the risk of recurrent or progressive thrombosis is estimated to exceed the risk of bleeding. Due to DOACs' increased risk for major bleeding events compared with low-molecular-weight heparins (LMWHs) in the venous thromboembolism treatment setting, LMWHs are generally the preferred agents in settings with an increased bleeding risk, especially in settings of relative contraindications. Patient preferences also need to be taken into consideration when making anticoagulation choices. ‡There is limited evidence regarding the safety of DOAC use in this setting. §The panel was not unanimous in the decision to list these as relative contraindications for DOAC, as we do not have adequate safety data in these clinical settings. Given the known increased risk in major and clinically relevant nonmajor bleeding for DOACs compared with LMWHs in the venous thromboembolism treatment setting, these relative contraindications for non-DOAC anticoagulants may be considered absolute contraindications for DOAC use in some patients.

TAKE HOME MESSAGES

- Cancer patients are at a high risk of VTE and have a high risk of VTE recurrence
- Cancer patients are at a higher risk of major bleeding
- Only 50% of patients adhere to long-term treatment with LMWHs
- Oral factor Xa inhibitors have demonstrated efficacy and safety in select cancer patients with CAT
- Oral factor Xa inhibitors may offer a more convenient and less invasive treatment option than LMWH for cancer-associated VTE
- In New Zealand rivaroxaban is the only registered and fully–funded oral factor Xa inhibitor
- LMWH is still the preferred option for patients with gastrointestinal cancer, particularly upper gastrointestinal cancer and certain genitourinary cancers
- Potential drug interactions with current systemic therapies must be considered before starting an anticoagulant
- International guidelines emphasise the importance of individualised treatment regimens and shared decision-making in the management of patients requiring anticoagulation for CAT
- VTE that is recurrent (2 or more) and provoked by active cancer should receive extended anticoagulation.

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