Cancer Associated Thrombosis Training Manual:

Management of patients with cancer-associated thrombosis (CAT)

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1.1 Aims

To complete the Cancer Associated Thrombosis (CAT) training programme to gain:

1) knowledge of CAT, its prevention and its treatment and,
2) the required advanced skills and competencies necessary to practice in a CAT clinic service.

1.2 Objectives

On completion of the CAT training programme you should be able to:

- Identify ambulant people with cancer (PWC) at risk of thrombosis and those who may benefit from primary thromboprophylaxis treatment.
- Advise on the most appropriate choice of anticoagulant for primary thromboprophylaxis.
- Advise on the most appropriate anticoagulant for the acute treatment of CAT.
- Advise on the most appropriate duration of anticoagulant treatment.
- Advise on the most appropriate anticoagulant for ongoing thromboprophylaxis in high risk patients beyond 6 months of treatment.
- Understand the differences between the terms minor-, clinically relevant non-major- and major bleeding
- Advise on the management of minor bleeding.
- Be aware of signs and symptoms which may indicate recurrent VTE and/or major bleeding and advise on appropriate management/referral.
- Be aware of the monitoring requirements for patients receiving anticoagulation and advise appropriately.
- Be competent in assessing different risks arising from the management and long-term impact of CAT using appropriate risk assessment tools.
- Be competent at guiding PWC through the patient information leaflet.
- Understand the views, preferences and values of PWC when dealing with anticoagulation.

2.0 Introduction

2.1 Cancer Associated Thrombosis

Venous thromboembolism (VTE), or as it has also been termed, cancer associated thrombosis (CAT), is a common complication in patients with cancer. CAT is the second leading cause of death in people with cancer (PWC), after the tumour itself, and the leading cause of death while receiving chemotherapy (i.e. higher than neutropenic sepsis) [1]. Studies have shown that 1 in 5 patients with cancer will develop a VTE during their cancer journey. Despite this, awareness of the condition in patients and healthcare professionals is low [2, 3].

VTE is an umbrella term that comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). The annual incidence of VTE in the general population is 117 per 100,000 people. Having cancer is associated with a 4.1 fold increased risk of VTE and receiving chemotherapy increases this risk to 6.5 fold. Overall, the approximate annual incidence of VTE in a population of PWC is 1 in 200 [1]. The annual death rate for CAT is 448 per 100,000 PWC, which equates to a 47 fold increase over the general population [4]. In addition, there is a 2.2 fold increase in mortality compared with patients with cancer without CAT [5].

CAT also causes significant morbidity in PWC, often resulting in hospitalisation and possible delay in cancer treatment. Patients with CAT are at an increased risk of recurrence (9.6 per 100 patient years), with the greatest risk of recurrence in the first few months following diagnosis [6, 7]. Additionally, the standard treatment for CAT, anticoagulant therapy, is associated with an increased risk of bleeding [8, 9].

Not all patients who develop CAT are symptomatic, with as many as half diagnosed incidentally following scans. The use of multi-slice computerised tomography (CT) in the diagnosis, staging and assessment of cancer treatment-response has led to an increase in the prevalence of incidental pulmonary embolism (IPE) in PWC [10, 11].

The prevention and treatment of thrombosis is an important aspect in the management of the long-term health of PWC. When caring for the ambulant PWC healthcare professionals need to be aware of the increased risk of thrombosis, the use of risk assessment scores and the risk-benefit profile of recommending anticoagulant therapy.

It is important to choose the most effective and the safest anticoagulant for the treatment of CAT to avoid morbidity and mortality. Thromboprophylaxis as primary prevention for CAT depends on factors such as the setting, bleeding and thrombotic risk factors, cost and quality of life (QOL) issues. In addition, the implementation of direct oral anticoagulants (DOACs), and their complex risk-benefit ratios have presented novel challenges for the treatment and prevention of CAT.

2.2 Risks Factors for Cancer Associated Thrombosis

Risk factors for the development of CAT can be both general and specific. Common risk factors are summarised in Table 1.

Table 1
Risk factors for the development of cancer associated thrombosis

Patient-related	Cancer-related	Treatment-related
• Increasing age • Sex (i.e. female) • Immobility; • Comorbidities (e.g. obesity, diabetes, chronic kidney disease, Charlson Comorbidity Index ≥3) • Previous venous thromboembolism • Familial hypercoagulability (first-degree relatives with VTE history) • Hereditary factors • Presence of varicose veins • Dehydration	• Cancer type (e.g. stomach, pancreatic, brain, lung, uterus, bladder, kidney, haematological) • Histological grade of tumour • Metastatic disease; • Time since cancer diagnosis • Presence of pro-coagulant molecules & inflammatory cytokines • Erythroid growth factors • Tumour compression	• Chemotherapy agents (e.g. cisplatin) • Chemotherapy combinations (e.g. ECF, FEC) ➢ iMIDS (e.g. thalidomide, lenalidomide) ➢ Hormonal therapy; (e.g. tamoxifen, stilboestrol); ➢ Anti-angiogenic therapy (e.g. bevacizumab, axitinib) ➢ Other therapies [e.g. high dose corticosteroids, marrow stimulating agents (GCSF, EPO)] ➢ Surgery ➢ Radiotherapy ➢ Central venous catheters ➢ Blood transfusion

Sources: [12] Ay *et al.* Thromb Haemost. 2017; 117: 219-230
[13] Fernandes *et al.* Eur Respir Rev. 2019; 28: 180119
[14] Power. Pharm. J. 2020; 305:7941
[15] NCCN Guideline V2.2023

Age

Older age is a risk factor for CAT, with risk increasing with advancing age. The highest risk is in patients aged 65 years and over [16].

Sex

Consensus around sex and risk of CAT have been conflicting with some studies showing a higher risk among those of female sex [16], while others have shown no link [7].

Immobility

Performance status (PS) has been shown to be an important prognostic marker in PWC [17] and evidence shows poorer PS increases the risk of CAT. Although, immobility is a common risk factor for CAT there is a lack of clinical consensus on the definition of immobility [18]. However, the International Society on Thrombosis and Haemostasis' (ISTH) definition [19] has been suitably applied to different patient cohorts at risk of VTE:

"Confined to bed in hospital (only 'bathroom privileges') for at least 3 days with an acute illness."

Cancer Type and Stage

Some cancers are associated with i) a very high risk of CAT e.g. pancreas (highest risk), stomach and brain, and ii) a high risk e.g. lung, haematological, gynaecological, renal and bladder. Metastatic disease in these malignancies further elevates the risk [7].

Time Since Cancer Diagnosis

Studies have shown the highest risk of developing CAT is in the immediate period post-diagnosis of cancer [20].

Systemic Anti-Cancer Therapy (SACT)

Receiving SACT significantly increases the risk of a patient developing CAT – there is a 6.5 fold increased risk, compared with a 4.1-fold risk in patients with cancer not receiving SACT [21]. Additionally, the risk is dependent upon the time period following initiation of chemotherapy, with studies showing an overall incidence of 7.3% after 3.5 months of treatment and 13.5% at 12 months [22]. The risk may vary according to the SACT agent, for example:

- Patients on cisplatin and 5-fluorouracil (5-FU) have a higher risk of VTE than patients on other chemotherapy agents [23]
- Targeted treatments of vascular endothelial growth factor (VEGF) are more likely to cause arterial clots [24]
- Immunomodulatory drugs (IMiDs) such as thalidomide and lenalidomide substantially increase the risk of VTE in myeloma patients [25]

However, when it comes to burden of VTE in the cancer treatment setting, it is the larger volume tumours such as breast cancer and prostate cancer, usually being treated with hormonal agents, that contribute most to the prevalence of CAT in the cancer population [26].

Other Therapies

The use of erythropoiesis stimulating agents (e.g. epoetin and darbepoetin) and corticosteroids also increase the risk of CAT [27, 28].

Central Venous Catheters

People with cancer often undergo insertion of central venous catheters (CVCs) to facilitate cancer management. This intervention has been associated with the development of clinically overt CVC-associated thromboembolism (CVCTE). Time to clot development seems to be short with the majority of CVCTEs happening within the first 60 days post-CVC insertion [29-31].

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3.0 Prevention of Cancer Associated Thrombosis

3.1 Background

PWC who may benefit from venous thromboembolism (VTE) prophylaxis include:

- Hospitalised patients (i.e., due to acute medical illness or surgery); and
- Ambulatory outpatients undergoing systemic anticancer therapy.

Both groups are potentially high-risk for VTE.

This training manual is concerned with ambulatory PWC undergoing systemic anti-cancer therapy only.

3.1.1 Current Guidance

The **National Institute for Health and Clinical Excellence (NICE)** does not currently recommend universal VTE prophylaxis in ambulatory PWC receiving cancer-modifying treatments [1].

Traditionally, LMWHs have been the standard of care for the prevention of CAT. A number of randomised controlled trials (RCTs) have been conducted in various cancer types to investigate the efficacy and safety of LMWH as primary thromboprophylaxis in ambulatory chemotherapy patients [2].

A meta-analysis of 26 RCTs involving 12,352 patients, showed that LMWH reduced the rate of symptomatic VTE in ambulatory PWC (risk ratio 0.54, 95% CI 0.38-0.75), but also increased bleeding risk (risk ratio 1.44, 95% CI 0.98-2.11) [2]. However, this risk was not statistically significant. The event rate in control groups was low and the absolute risk reduction with prophylactic LMWH was 2-3%.

However, there are patient groups where VTE prophylaxis needs to be considered:

1. Patients with myeloma receiving chemotherapy with steroids and an immunomodulatory imide drug (IMiDs) such as thalidomide, pomalidomide or lenalidomide.

For these patients, **NICE** recommends considering pharmacological thromboprophylaxis with either aspirin (75mg or 150mg) or low molecular weight heparin (LMWH).

The British Society for Haematology (BSH) expanded this further by recommending patients with a low risk use aspirin and those at high risk use LMWH [3].

The **Scientific and Standardization Committee (SSC)** suggest LMWHs to be preferred in patients with additional risk factors such as a history of VTE. The SSC also suggest the duration of primary thromboprophylaxis to be during the duration of thalidomide-, pomalidomide- or lenalidomide-based treatment [4].

Studies have shown an increased risk of VTE in patients with myeloma as high as 10% per year [5]. Currently, there is no universally recommended risk assessment tool for assessing VTE risk in patients with myeloma. However, the *IMPEDE-VTE* risk assessment tool has been validated in this patient group [6]. The score involves assessing risk based on:

- IMiDs treatment (+4)
- Body mass index ≥ 25 kg/m^2 (+1)
- Pelvic/hip fracture (+4)
- Erythropoietin use (+1)
- Dexamethasone [low dose ≤160mg pm (+2), high dose > 160mg pm (+4)] / Doxorubicin treatment (+3)
- Asian Ethnicity (-3)
- VTE history prior to myeloma diagnosis (+5)
- Tunnelled/central venous catheter (+2)
- Existing thromboprophylaxis [therapeutic dose (-4), prophylactic dose or aspirin (-3)]

A 1-point increase in the score was associated with an increased risk of VTE 1.2-fold. High-risk patients with a score of >3 should be considered for VTE prophylaxis with anticoagulation. Low risk patients should receive either no VTE prophylaxis or aspirin (75-150mg OD). However, this score is not without limitations, including its level of accuracy and ability to distinguish between aspirin *vs*. LMWH. Additional external validation work has added to support use of this risk assessment tool [7]. However, more work is needed to determine optimal choice of VTE prophylaxis (including use of DOACs) as well as the potential of adding additional haemostatic biomarkers to the risk assessment process.

In 2008, the **International Myeloma Working Group (IMWG)** published guidance on the prevention of IMiD-associated thrombosis in myeloma recommending that all patients be assessed for risk and offered thromboprophylaxis with LMWH if they have ≥2 thrombosis risk factors or if they are receiving concurrent IMiDs and high-dose corticosteroids, whereas those with ≤1 risk factors should be offered aspirin [8]. Individual risk factors for thrombosis associated with thalidomide/lenalidomide-based therapy include age, history of VTE, CVC, comorbidities (infections, diabetes, cardiac disease), immobilisation, surgery and inherited thrombophilia. Myeloma-related risk factors include diagnosis and hyper-viscosity.

A retrospective review involving 70 patients has shown that apixaban at a prophylactic dose of 2.5mg twice daily may be as effective and comparable to other traditional forms of VTE prophylaxis when used in myeloma patients undergoing chemotherapy with IMiDs/steroids [9]. Apixaban was prescribed for at least 4 months or until completion of the patient's chemotherapy. Rates of thrombosis were very low with no cases of VTE identified and only two cases of arterial thrombosis. There was one episode of major bleeding associated with thrombocytopenia.

2. Patients with advanced pancreatic cancer who are receiving systemic anti-cancer treatment.

NICE recommends pharmacological VTE prophylaxis with LMWH to be considered.

This recommendation is based upon the high rate of CAT in this specific group of patients (between 20 – 60%) and the potential benefit of VTE prophylaxis. The *CONKO-04 study* showed that LMWH (i.e. enoxaparin 1mg/kg once daily) use in patients with pancreatic cancer undergoing chemotherapy produced a 6.4% overall cumulative incidence rate of symptomatic CAT, compared with a rate of 15.1% in the comparator arm (hazard ratio [HR] 0.40; 95% confidence interval [CI]: 0.19–0.83; P =0.01) [10].

Subsequently, the *FRAGEM study* evaluated the impact of dalteparin at a dose of 200 units/kg once per day for four weeks, followed by 150 units/kg once per day for eight weeks being added to gemcitabine for the treatment of pancreatic cancer. Similar findings were observed to *CONKO-04* and the rate of symptomatic VTE reduced from 23% to 3.4% (risk ratio 0.145; 95% CI: 0.035–0.612) with a similar rate of bleeding [11].

American Society of Clinical Oncology (ASCO) recommends that a risk-adapted approach to thromboprophylaxis in ambulatory patients receiving cancer treatment should be accompanied by a discussion with patients of the balance between absolute benefits and harms as well as the uncertainty surrounding duration of prophylaxis [12].

3. High-risk outpatients with cancer (Khorana score of 2 or higher) prior to starting a new systemic anti-cancer treatment.

ASCO recommends that these patients be offered thromboprophylaxis with apixaban, rivaroxaban or LMWH, provided there are no significant risk factors for bleeding and no drug-drug interactions [12].

The **American Society of Haematology (ASH)** also recommends consideration of VTE prophylaxis for PWC deemed to be at intermediate or high risk of VTE [13]. **ASH** recommends consideration of a DOAC as prophylaxis for those patients at intermediate or high risk of VTE. LMWH prophylaxis is only recommended as an option for those at high risk.

Decision-making should be made using a validated risk assessment tool in conjunction with clinical judgement and experience. The suggested risk assessment tool is the Khorana score. **ASH** highlights that more research is needed in this area to determine harms and benefits by tumour type. Even those patients with a high risk of VTE should receive VTE prophylaxis with caution if there is a high risk of bleeding.

The **ISTH-SSC** has issued the following guidance on the use of DOACs [14]:

- DOACs are suggested as the primary thromboprophylaxis in ambulatory PWC starting chemotherapy who have a Khorana score ≥ 2, no drug-drug interactions and are not at high risk for bleeding.
- The final decision should be made with the patient with consideration of the risks and benefits of thromboprophylaxis.
- Duration of thromboprophylaxis should be up to 6 months after initiation of chemotherapy.
- Platelet counts and risk of bleeding complications should be monitored for the duration of anticoagulation.
- Where there are concerns about the safety of the use of DOACs (e.g. significant drug-drug interactions with DOACs, high risk of gastrointestinal (GI) bleeding) LMWHs are to be used in high-risk ambulatory PWC.

These guidelines are based on the AVERT and CASSINI studies [15, 16]. Both studies examined the use of thromboprophylaxis in high-risk (Khorana score ≥2) ambulatory patients with cancer starting chemotherapy using either apixaban 2.5mg twice daily (AVERT) and rivaroxaban 10mg daily (CASSINI) for 180 days *vs.* placebo.

In the AVERT study, the primary efficacy outcomes were the occurrence of symptomatic proximal DVT of upper or lower extremities, symptomatic or incidental PE or VTE related death [15]. The primary safety outcome was major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH). Use of apixaban in the AVERT study was associated with a significantly lower incidence of VTE than placebo (4.2% *vs*. 10.2%, number-needed-to-treat [NNT] = 17), but with a higher incidence of major bleeding episodes (3.5% *vs*. 1.8%, number-needed-to-harm [NNH] = 59). Bleeding episodes were predominantly in patients with gastrointestinal or gynaecological malignancies.

In the CASSINI study, the primary efficacy outcomes were symptomatic or screen-detected proximal lower extremity DVT or PE, symptomatic upper or lower extremity distal DVT or VTE related death [16]. The primary safety outcome was ISTH-defined major bleeding. Use of rivaroxaban in the CASSINI study resulted in a non-significant 2.8% absolute reduction in risk of VTE *vs*. placebo. Of note 47% of patient discontinued rivaroxaban early for numerous reasons. However, in a pre-specified intervention-period analysis (i.e. time on drug only considered) there was a significant

absolute reduction in risk of VTE of 3.8%. There was no significant difference in major bleeding (2% with rivaroxaban *vs*. 1% with placebo).

A pooled analysis of the two studies has shown a 6-month reduction in VTE risk of 0.56 (95% CI 0.35-0.89), equating to an absolute reduction in VTE risk of 4% (95% CI 0.01–0.07, NNT 25) [17]. There was a non-significant increase in major bleeding 1.96 (95% CI 001-.007, NNT = 15), equating to an absolute increase of 1% (95%CI 0.0–0.02, NNH = 100). This compares favourably with previous studies involving LMWH, but which may have been affected by patient selection [18].

It is also worth noting the high adherence rates for the on-treatment arms of both studies (98.4% in CASSINI and 83.6% in AVERT). Adherence with therapy is obviously important to ensure efficacy of therapies.

3.1.2 Assessment of Thrombotic Risk

It is important to practice risk stratification to identify PWC in high-risk groups and recommend thromboprophylaxis to improve the risk-benefit ratio and reduce number needed to treat (NNT). This is particularly important given that cancer is also associated with an increased risk of bleeding. Furthermore, depending on the choice of anticoagulant there may also be potential for interaction with anti-cancer therapy or the burden of administering daily injections.

ASCO recommends conducting a risk-assessment of VTE using an assessment tool, such as the Khorana score (Table 2). This validated tool estimates the risk of VTE in ambulatory patients with cancer receiving chemotherapy. The Khorana score considers cancer type, blood counts and body mass index (BMI) to predict the likelihood of a patient developing a CAT.

Patients are divided into three risk groups, which allow healthcare professionals to evaluate whether anticoagulation should be considered.

Table 2 The Khorana Score	
Risk factor	**Points**
Site of primary tumour - Very high risk (stomach, pancreas) - High risk (lung, lymphoma, gynaecologic, bladder, testicular) - All other sites	 2 1 0
Pre-chemotherapy platelet count ≥350 x 10^9/L	1
Haemoglobin level <100g/L or use of erythropoiesis-stimulating agents	1
Pre-chemotherapy WBC >11 x 10^9/L	1
Body mass index (BMI) ≥35kg/m^2	1
Risk groups: - **Low risk = 0** - **Intermediate risk = 1-2** - **High risk = >3**	
Source: [19] Khorana, A.A. et al. (2008). Blood, 111(10), 2008;111:4902-4907.	

However, this score has only baseline assessment value, does not optimally stratify many patients (particularly patients with lung cancer) and a number of efforts to optimise the score have not resulted in a universally accepted risk-adaptive management score (RAM) [20].

The most promising score in terms of simplicity and being usable in a longitudinal sense is the catscore [21], derived from the Vienna Cancer and Thrombosis Study. This only uses two variables: cancer site (as described for the Khorana score) and D-dimer as a continuous variable. This model was successfully found to predict risk of VTE in PWC with solid tumours and found to be an improvement on previous models and has been validated.

As things stand the preferred tool for cancer patient stratification is the catscore, though this necessitates ordering a D-dimer test. A link to the risk assessment tool can be found here:

https://practical-haemostasis.com/Clinical%20Prediction%20Scores/Formulae%20code%20and%20formulae/Formulae/VTED-Cancer/CATS_score.html

3.1.3 VTE Prophylaxis for Central Venous Catheters

A Cochrane review evaluating the efficacy of oral and parenteral anticoagulants in the prevention of CVC-related VTE was carried out in 2018 [22]. This review found moderate-certainty evidence that prophylactic LMWH reduces catheter-related VTE

compared to no LMWH. There was inconclusive evidence on the effect of LMWH prophylaxis on mortality or the effect of warfarin on mortality or risk of catheter related VTE. It is not clear if DOACs are beneficial in the prevention of CVC related thrombosis. The routine use of anticoagulants at prophylactic or therapeutic dose to prevent catheter related VTE in patients with cancer is not currently recommended due to this uncertainty.

3.2 Anticoagulant Therapy for the Prevention of CAT

3.2.1 LMWHs: Dalteparin, Enoxaparin and Tinzaparin

3.2.1.1 Dosing

It is important to note that all dosing regimens described below are, at the time of writing, unlicensed in the UK.

3.2.1.1.1 General Prophylactic Dosing

The doses used in ambulatory thromboprophylaxis of oncology patients are generally the same as those used for prophylaxis of VTE in medical inpatients.

Dalteparin: 5,000 units via subcutaneous injection once a day. In patients with a CrCl of <30ml/min, dosing should be based on anti-Xa levels [23] (though these low doses rarely accumulate to a degree to cause substantial bleeding risk).

Enoxaparin: 40mg via subcutaneous injection once a day (reduced to 20mg in patients with a CrCl of <30ml/min).

Tinzaparin: 4,500 units via subcutaneous injection once a day (no dose adjustment required down to a CrCl of 20 ml/min).

3.2.1.1.2 Specific Scenario Dosing

As discussed in Section 3.1, studies investigating the use of ambulatory thromboprophylaxis in pancreatic patients receiving gemcitabine-containing regimes used different dosing strategies to those outlined above. These are:

CONKO-004 Regime (Enoxaparin): Enoxaparin 1mg/Kg OD for 3 months, then 40mg OD until disease progression (see below for option beyond 3 months).

Initial enoxaparin dose was reduced to 0.5mg/kg in patients with a platelet count of between 50 and $75x10^9$/L. Those with lower platelet counts were excluded.

It should be noted that patients weighing less than 45kg or more than 100kg, and those with a CrCl of less than 30ml/min were excluded from this study.

FRAGEM Regime (Dalteparin): Dalteparin 200 units/kg once per day for four weeks, followed by 150 units/kg once per day for eight weeks.

It is important to note that the data for both high dose LMWH schedules is limited to three months.

One can consider switching to a DOAC after three months of increased dose LMWH thromboprophylaxis given that PDAC patients are by definition Khorana score 2 at least and by extension the AVERT or CASSINI data are relevant to these patients till at least 6 months from commencement of thromboprophylaxis.

3.2.1.2 Cautions/Contraindications

Absolute

- Hypersensitivity to heparin or its derivatives, including other LMWH or to any of the excipients.
- Current or previous immune mediated heparin-induced thrombocytopenia (HIT).
- Active clinically significant bleeding and conditions with a high risk of haemorrhage, including recent haemorrhagic stroke, gastrointestinal ulcer, presence of malignant neoplasm at high risk of bleeding, recent brain, spinal or ophthalmic surgery, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intra-spinal or intracerebral vascular abnormalities.
- Spinal or epidural anaesthesia or loco-regional anaesthesia when used for prophylaxis in the previous 4-6 hours or next 12 hours.

Concurrent use of anticoagulants known to increase the risk of bleeding, e.g. DOAC, warfarin INR >2.

Relative

- Bacterial endocarditis, pericarditis, thoracic aneurysm.
- Uncontrolled systolic hypertension ≥ (230/120mmHg or higher).
- Thrombocytopenia (Platelet count $<75x10^{-9}$/L).
- Be aware that LMWHs are of animal origin, and this may be of concern to some people [24]. Discuss the alternatives with people who have concerns about

using animal products, after discussing their suitability, advantages and disadvantages with the patient [1].

- Caps on the bottles of dalteparin can contain latex – check whether the patient has a latex allergy.

3.2.1.3 Monitoring

There is no formal guidance on monitoring of LMWHs as thromboprophylaxis agents in PWC. Baseline urea and electrolytes, full blood count (FBC) and liver function tests (LFTs) are recommended. Thereafter, monitoring will be dependent on clinical parameters.

3.2.1.3.1 Renal Function

As above there is no formal guidance on how often to check renal function. A pragmatic approach would be to consider:

- If the patient's renal function is stable (and >30ml/min), three to six monthly monitoring is appropriate.
- If the patient's renal function is below 30 ml/min and erratic, consider two monthly monitoring.
- If changes in renal function will have implications for dosing, consider monthly monitoring.

Dose adjustments based upon renal function are summarised below (Table 3):

Table 3: Dose adjustments of LMWH based upon renal function

	Tinzaparin	Enoxaparin	Dalteparin
Full dose	4,500 units If CrCl ≥ 20ml/min	40mg OD if CrCl ≥ 30ml/min	5,000 units OD if CrCl >30ml/min
Reduced dose	If CrCl < 20ml/min: No recommendation. Some studies use 3,500 UNITS (off-license)	If CrCl 15-30ml/min: 20 mg/kg OD If CrCl <15ml/min: use is not recommended, however renal drug handbook support use of 20mg dose with caution	Consider monitoring if CrCL <20ml/min and on a prolonged course (e.g. > 2 weeks). Alternatively, consider reducing the dose to 2,500 units or using unfractionated heparin 5,000 units SC BD.

3.2.1.3.2 Potassium

Heparin products can have an impact on potassium via suppression of adrenal secretion of aldosterone, leading to hyperkalaemia. Risk factors for heparin-induced hyperkalaemia include:

- Diabetes mellitus
- Chronic renal failure
- Pre-existing metabolic acidosis
- Raised plasma potassium at pre-treatment
- Use of concomitant medication that may also increase serum potassium

Patients should have their potassium monitored at baseline, within a month, and three to six monthly thereafter. In the event of hyperkalaemia developing, an alternative anticoagulant should be considered. It is usually reversible on discontinuation of LMWH.

3.2.1.3.3 Platelets

There is no formal guidance on how often to check platelets on prophylactic doses of LMWH.

HIT is a rare but potentially life threating complication of heparin usage, although thankfully it is very uncommon with LMWH.

3.2.1.3.4 Osteoporosis Risk

LMWH is a known risk factor for the development of osteoporosis. Data is limited; however it seems to be that use of LMWH up to 6 months may not increase risk of osteoporosis but use up to 24 months may reduce bone mineral density (BMD), however this remains unclear. Therefore, it is recommended that patients who require ongoing LMWH beyond 24 months, who have other risk factors for fragility fractures, should have their BMD assessed.

3.2.2 DOACs: Apixaban and Rivaroxaban

At the time of writing only apixaban and rivaroxaban have data for use as ambulatory thromboprophylaxis in PWC, however the use of these therapies in this setting remains unlicensed.

3.2.2.1 Dosing

Apixaban: 2.5mg twice a day.

Rivaroxaban: 10mg once a day.

It is important to note that the data for both therapies is limited to six months.

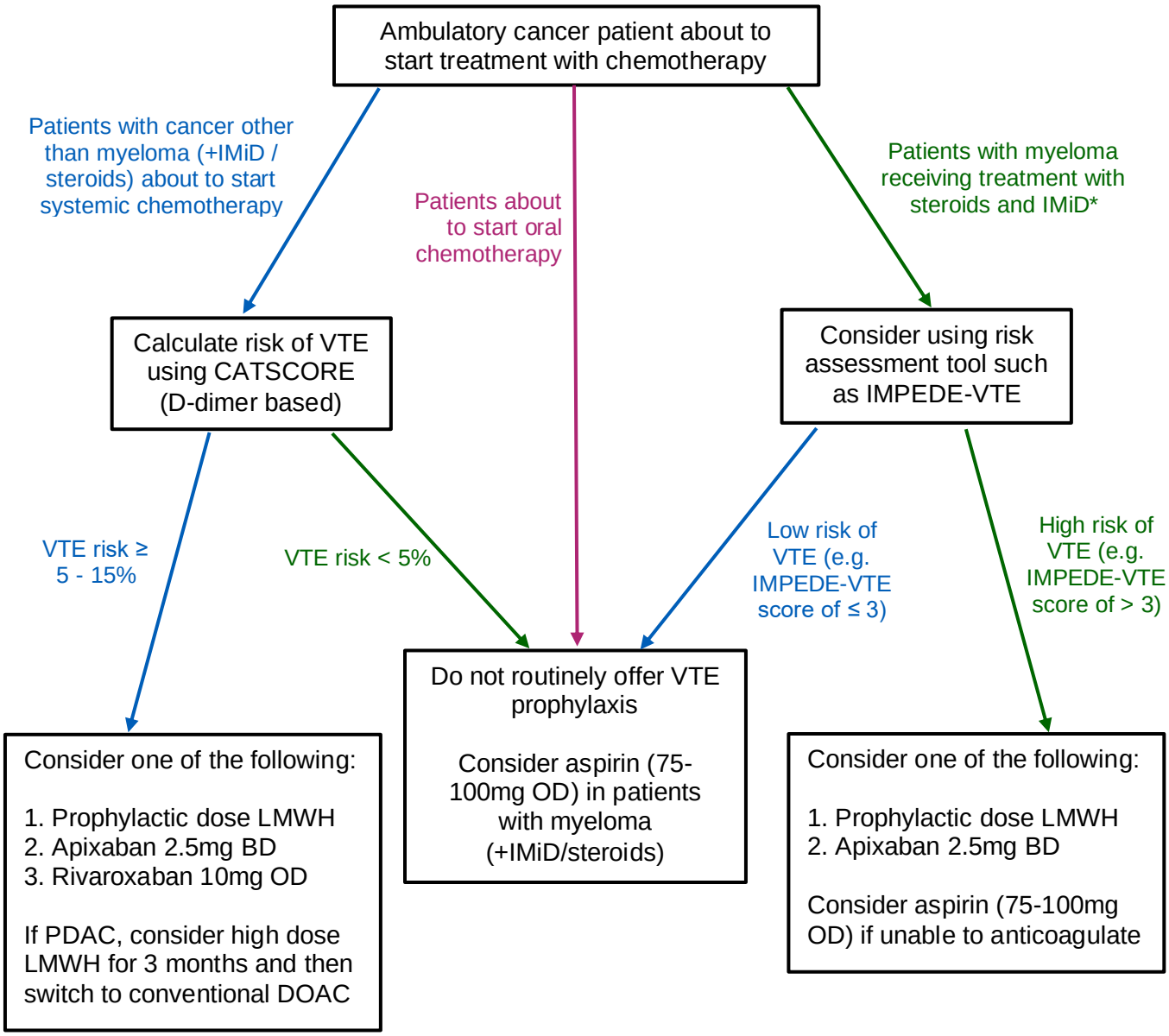
3.2.2.2 Cautions/Contraindications

- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition if considered a significant risk factor for major bleeding. It should be noted that concerns regarding bleeding and the use of DOAC's exist in those patients with gastro-intestinal or genitourinary cancers with an intact primary.
- Concomitant treatment with any other anticoagulant agent.

3.2.2.3 Monitoring

There is no formal guidance on monitoring of DOACs as thromboprophylaxis agents in PWC. Baseline urea and electrolytes, FBC and LFTs are recommended. It would be a sensible approach to review pre- and post-chemotherapy bloods.

Flow diagram 1: Decision making tool for VTE prophylaxis in cancer patients starting chemotherapy



**Immunomodulatory imide drugs such as thalidomide, pomalidomide or lenalidomide*
In all instances where VTE prophylaxis is considered, be aware and consider the potential risk of bleeding on an individual patient basis

3.3 Summary of Main Points

- Ambulatory PWC have variable risks of VTE. It is important to practice risk stratification to identify PWC in high-risk groups using validated risk assessment models. We recommend the catscore for solid malignancies if D-dimer measurement is available (consider the Khorana Score if not) and the IRWG stratification of myeloma patients.
- NICE recommends that thromboprophylaxis is not considered in ambulatory PWC receiving cancer-modifying treatments unless they are at risk of VTE because of something other than cancer.
- There are two exceptions to this:
    - Myeloma patients who are receiving chemotherapy with thalidomide, pomalidomide or lenalidomide with steroids should be considered for thromboprophylaxis with aspirin or LMWH.
    - People with pancreatic cancer who are receiving chemotherapy should be considered for thromboprophylaxis with LMWH at an increased dose (PDAC patients are almost invariably classified as high risk on catscore or Khorana score).
- High-risk outpatients with cancer should be considered for thromboprophylaxis with apixaban, rivaroxaban or LMWH, provided there are no significant risk factors for bleeding and no drug interactions.
- DOACs such as rivaroxaban or apixaban, can be used as long as there is no significant drug-drug interaction or high risk of GI bleeding.
- If there is a concern of significant drug-drug interaction or a high risk of GI bleeding, LMWHs are acceptable alternatives for primary thromboprophylaxis.
- Routine use of anticoagulants at prophylactic or therapeutic dose to prevent catheter-related thrombosis in patients with cancer is not recommended.

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4.0 Treatment of Cancer Associated Thrombosis

4.1 Background

It is important to initiate the most effective and safe anticoagulant in the management of CAT to avoid CAT-related mortality and morbidity.

An individualised, risk-adapted approach must be taken. The risk/benefit ratio (e.g. risk of bleeding, risk of recurrent VTE), possible drug-drug interactions, the patient's preference and additional factors (e.g. weight, clinical complications such as thrombocytopenia) should be considered when making treatment decisions.

When offering anticoagulation treatment, follow the recommendations on shared decision making and supporting adherence in the NICE guidelines [1, 2].

Treatment for CAT can be with either low molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC). Research trials have suggested that LMWH is superior to warfarin / vitamin K antagonists (VKA) and that DOACs are non-inferior to LMWH.

4.1.1 Current Guidance

NICE recommended in the 2020 published guidelines (NG158) [3]:

- PWC with confirmed DVT or PE should be offered anticoagulation treatment for 3 to 6 months. This should be reviewed at 3 or 6 months based on clinical need. It is good practice to determine the length of treatment on a case-by-case basis.
- When choosing anticoagulation treatment for CAT, consider the tumour site, interactions with other drugs including those used to treat the cancer and the risk of bleeding.
- If suitable, a DOAC should be considered for the treatment of CAT. Due to limited evidence, NICE cannot currently give more specific recommendations about the choice of DOAC. However, the 2023 **ASCO** guidelines recommend apixaban as an option for the treatment of VTE [4]. This is a strong recommendation based on high-quality evidence.
- Evidence suggests a higher rate of GI and genitourinary bleeds in PWC having treatment with a DOAC compared with those having LMWH. DOACs may be unsuitable for patients with tumours that are associated with an increased risk of these types of bleeds.
- If a DOAC is not suitable, consider LMWH alone. In certain circumstances (e.g. healthcare systems, costs etc.), LMWH concurrently with a VKA for at least 5 days, or until the international normalised ratio (INR) is at least 2.0 in 2 consecutive readings, followed by a VKA on its own is an acceptable option.

The **ISTH SSC** has issued the following guidance on the treatment of CAT [5]:

- LMWHs are suggested for PWC with an acute diagnosis of VTE and a high risk of bleeding. This includes patients with luminal GI cancers with an intact primary tumour and patients with active GI mucosal conditions (e.g. duodenal ulcers, gastritis, esophagitis or colitis).
- DOACs are suggested for PWC with an acute diagnosis of VTE, low risk of bleeding and no drug-drug interactions with current systemic therapy.
- LMHWs remain an acceptable alternative for these patients.

The **American College of Chest Physicians (CHEST)** 2021 Guidelines [6] recommend a DOAC (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy for PWC with CAT.

The use of DOACs is off label for the treatment of upper-limb DVT. However, **BSH** guidelines for the management of venous thrombosis at unusual sites recommend that patients with upper-limb DVT should receive anticoagulation with heparin for at least 5 days and warfarin. The optimal duration of warfarin therapy is unknown. Periods of 3 to 6 months are associated with low risk of recurrence and are likely to be satisfactory [7].

4.1.2 Low Molecular Weight Heparin

Much like for the prevention of CAT, traditionally, LMWHs have been the standard of care for the treatment of CAT.

Two RCTs were conducted comparing the efficacy of managing VTE with LMWHs to VKAs [8, 9].

The CLOT trial, involving 676 PWC, compared 6 months of weight adjusted dalteparin (200IU/kg for one month then 150 IU/kg for 5 months) with 5 days weight adjusted dalteparin followed by a total of 6 months VKA [8]. The primary efficacy endpoint was recurrent VTE, PE or both. The safety endpoints were major bleeding or any other bleeding. Dalteparin was more effective in preventing recurrent thromboembolism compared to VKA (HR, 0.48; P=0.002). There was no statistical difference in bleeding rates.

The CATCH trial, which included 900 PWC, compared tinzaparin (175 IU/kg) once daily for 6 months vs conventional therapy with tinzaparin (175 IU/kg) once daily for 5 to 10 days followed by warfarin [9]. The primary efficacy endpoint was recurrent VTE or PE. The primary safety endpoints were major bleeding and clinically relevant non-major bleeding (CRNMB). Similar to the CLOT trial, there was a lower rate of VTE recurrence in the LMWH arm (HR, 0.65 [95% CI, 0.41-1.03]; P = .07) however, this did not achieve statistical significance. There were no differences in major bleeding but a significant reduction in CRNMB was observed with tinzaparin.

Compared to VKAs, LMWH are associated with a lower risk of recurrent thrombosis without an increase in risk of bleeding. For this reason, LMWH were the anticoagulation treatment of choice over VKAs, until the recent introduction of DOACs.

4.1.3 Direct Oral Anticoagulants

Randomised clinical trials have compared the use of **DOACs** to **LMWHs**.

In the Hokusai VTE Cancer study, edoxaban was compared to dalteparin [10]. The primary outcome was a composite of recurrent VTE and major bleeding. The secondary outcomes were CRNMB, death and event-free survival (EFS). Edoxaban was shown to be non-inferior to dalteparin for the composite outcome of recurrent VTE and major bleeding in 1,050 PWC with CAT. The absolute rate of recurrent VTE was 3.4% lower with edoxaban, whereas the absolute rate of major bleeding was 2.9% higher. However, further scrutiny of the major bleeding events showed that, while the higher number of bleeds occurred in patients on edoxaban, the more severe outcomes occurred in those on dalteparin. Importantly, most of the major bleeding with edoxaban occurred in patients with GI cancer and so DOACs should be used carefully in patients with these types of cancer.

SELECT-D was a randomised, open-label, pilot trial involving patients with active cancer who had symptomatic PE, IPE or symptomatic lower-extremity proximal DVT [11]. Patients were randomised to either rivaroxaban (15 mg BD for 3 weeks, then 20 mg OD for a total of 6 months) or dalteparin (200 IU/kg daily during month 1, then 150 IU/kg daily for months 2-6). The primary outcome was VTE recurrence over 6 months and the safety outcome was assessed by major bleeding and CRNMB. Similarly to Hokusai VTE, the DOAC reduced VTE recurrence but at the cost of increased bleeding compared with the LMWH (Table 4).

Table 4: Results from the SELECT-D Pilot Trial

SELECT-D Pilot Study	Rivaroxaban (N = 203)	Dalteparin (N = 203)
Recurrent VTE, n (%)	8 (4)	18 (11)
Major bleeding, n (%)	11 (5)	6 (3)
CRNMB, n (%)	25 (12)	7 (3)
Major and CRNMB, n (%)	36 (17)	12 (6)

In the ADAM VTE trial patients with CAT were randomly assigned to receive treatment with either apixaban 10 mg BD for seven days followed by 5 mg BD for six months or subcutaneous dalteparin (200 IU/kg for one month followed by 150 IU/kg OD) [12]. Out of 287 patients, recurrent VTE occurred in 0.7% of apixaban treated patients compared to 6.3% of dalteparin patients [HR 0.099, 95% CI, 0.013-0.780, P = .0281). For the primary bleeding endpoint, major bleeding occurred in 0% of 145 patients receiving apixaban compared with 1.4% of 142 patients receiving dalteparin.

However, the secondary composite endpoint of major bleeding and CRNMB 6% of patients in each arm had an event.

The Caravaggio trial was another randomised study of apixaban (10 mg BD for the first 7 days, followed by 5 mg BD up to 6 months) compared to subcutaneous dalteparin (200 IU/kg OD for the first month, followed by 150 IU/kg OD up to 6 months) [13]. Recurrent VTE occurred in 32 of 576 patients (5.6%) in the apixaban group and in 46 of 579 patients (7.9%) in the dalteparin group (HR, 0.63; 95% CI, 0.37 to 1.07; P<0.001 for noninferiority). Major bleeding occurred in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the dalteparin group (HR, 0.82; 95% CI, 0.40 to 1.69; P = 0.60). Therefore, oral apixaban is a relatively safe option for the treatment of CAT.

4.2 Anticoagulant Therapy for the Treatment of CAT

4.2.1 LMWHs: Dalteparin, Enoxaparin and Tinzaparin

4.2.1.1 Dosing

Dalteparin	
For the extended treatment of VTE and prevention of recurrence in patients with solid tumours by subcutaneous injection	
For adult by body weight	**Dose**
40 - 45 kg	7500 units once daily for 30 days, then 7500 units once daily for a further 5 months.
46 - 56 kg	10 000 units once daily for 30 days, then 7500 units once daily for a further 5 months.
57 - 68 kg	12 500 units once daily for 30 days, then 10 000 units once daily for a further 5 months.
69 - 82 kg	15 000 units once daily for 30 days, then 12 500 units once daily for a further 5 months.
83 - 98 kg	18 000 units once daily for 30 days, then 15 000 units once daily for a further 5 months.
99 kg and above	18 000 units once daily for 30 days, then 18 000 units once daily for a further 5 months.
Note for all doses: **Interrupt treatment or reduce dose in cases of chemotherapy-induced thrombocytopenia.**	
[14] **https://bnf.nice.org.uk/drugs/dalteparin-sodium/#indications-and-dose**	

Enoxaparin	
For the treatment of DVT and PE by subcutaneous injection	
For adult	1 mg/kg every 12 hours until adequate oral anticoagulation established.
[15] **https://bnf.nice.org.uk/drug/enoxaparin-sodium.html#indicationsAndDoses**	

Tinzaparin	
For the treatment of DVT and PE by subcutaneous injection	
For adult	175 units/kg once daily until adequate oral anticoagulation established, treatment regimens do not require anticoagulation monitoring.
For the extended treatment of VTE and prevention of recurrence in patients with active cancer by subcutaneous injection	
For adult	175 units/kg once daily for 6 months; the benefit of continued treatment beyond 6 months should be evaluated.
[16] **https://bnf.nice.org.uk/drugs/tinzaparin-sodium/#indicationsAndDoses**	

4.2.1.2 Cautions/Contraindications

4.2.1.2.1 All LMWHs

- Acute bacterial endocarditis
- After major trauma
- Epidural anaesthesia with treatment doses
- Haemophilia or other haemorrhagic disorders
- Peptic ulcer
- Recent cerebral haemorrhage
- Recent surgery to eye
- Recent surgery to nervous system
- Severe hypertension
- Spinal anaesthesia with treatment doses
- Thrombocytopenia (including history of heparin-induced thrombocytopenia).

4.2.1.2.2 Dalteparin

- Mechanical prosthetic heart valve

4.2.1.3 Monitoring

Routine monitoring is not required with LMWHs. However, anti-Xa assay can be used to monitor patients in cases of extremes of weight, renal failure or VTE despite treatment with LMWH.

4.2.2 DOACs: Apixaban, Edoxaban and Rivaroxaban

DOACs are a recent admission to the treatment options available to patients being treated for CAT. DOACs are seen as a convenient option to their injectable alternatives. Since the publication of the Hokusai-VTE cancer (edoxaban) [10], SELECT-D (rivaroxaban) [11] and Caravaggio (apixaban) [13] studies, DOACs are now recommended as first line therapies in numerous international societal guidelines. However, the aforementioned studies highlighted some bleeding concerns, specifically with edoxaban and rivaroxaban in patients with luminal gastrointestinal or genitourinary malignancies with an intact primary. As such, use is discouraged in these patient groups.

4.2.2.1 Apixaban

4.2.2.1.1 Dose and administration [17, 18]

Day 1 to 7	Day 8 to 180	Day 181 onwards
10mg BD	5mg BD	2.5mg BD [a]

[a] 2.5mg BD is the licensed dose of apixaban in patients who required extended anticoagulation for long term prevention of VTE. At the time of writing there are no dedicated studies in people with cancer for the use of apixaban 6 months post index event, however studies are currently being undertaken to address the issue.

Renal Function (CrCl)	Dose
≥30ml/min	Use standard dose regime
<30ml/min but ≥ 15ml/min	Use standard dose regime with caution
<15ml/min	Contraindicated

Apixaban is only available in a solid oral dosing form (tablets). It may however be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree, for patients with swallowing difficulties.

For those with nasogastric (NG) tubes, tablets may be crushed and suspended in 60 mL of water or G5W.

There are no theoretical stability concerns around apixaban being stored in a compliance aid.

4.2.2.1.2 Contraindications

- Hypersensitivity to the active substance.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition if considered a significant risk factor for major bleeding. This may include current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding (see above), recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agent.
- Pregnancy and breast feeding.

4.2.2.1.3 Monitoring

There are no specific monitoring requirements for apixaban.

It is good practice to check renal function, hepatic function and full blood count prior to starting therapy.

There is no formal guidance around how often to re-check these parameters, however good practice guidelines for atrial fibrillation (AF) recommend checking hepatic function and full blood count annually. A useful guide for checking renal function is to follow the rule of dividing the creatinine clearance by 10, i./e. a CrCl of 40ml/min would necessitate four monthly repeat checks [19].

It should be noted however that due to the complexity of oncology patients, clinical judgement is often indicated. Patients on highly myelosuppressive chemotherapy regimens may be more at risk of anaemia or thrombocytopenia, hence individualised monitoring schedules should be developed.

4.2.2.1.4 Interactions

Concomitant therapies which have strong inhibitory / induction effects on both P-glycoprotein (P-gp) and CYP3A4 are generally contraindicated with apixaban [21].

Therapies that either have strong effects on one of these systems or have a moderate effect on both of these systems are generally cautioned with apixaban.

For further information consult the product summary of product characteristics (SmPC).

4.2.2.2 Edoxaban

4.2.2.2.1 Dose and administration [20, 21]

Until at least day 5	Day 5 to 180	Day 181 onwards
LWMH therapy at a treatment dose (see above)	60mg OD	60mg OD

Dose recommendation for patients with one or more of the following clinical factors:		
Renal impairment	Moderate or severe (CrCl 15 – 50 mL/min)	30 mg edoxaban once daily
Low body weight	≤ 60 kg	
P-gp inhibitors	Ciclosporin, dronedarone, erythromycin, ketoconazole	

Edoxaban is only available in a solid oral dosing form (tablets).

For patients who are unable to swallow whole tablets, edoxaban tablets may be crushed and mixed with water or apple puree and immediately administered orally.

Alternatively, Lixiana tablets may be crushed and suspended in a small amount of water and immediately delivered through a gastric tube after which it should be flushed with water. Crushed Lixiana tablets are stable in water and apple puree for up to 4 hours.

There are no theoretical stability concerns around rivaroxaban being stored in a compliance aid.

4.2.2.2.2 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Clinically significant active bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent GI ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

- Uncontrolled severe hypertension.
- Concomitant treatment with any other anticoagulants.
- Pregnancy and breast feeding.

4.2.2.2.3 Monitoring

See apixaban section 4.2.2.1.3.

4.2.2.2.4 Interactions

Concomitant therapies which have strong inhibitory / induction effects on P-gp are generally contraindicated with Edoxaban [22].

Therapies that have strong have a moderate effect on this system are generally cautioned with Edoxaban.

For further information consult the product summary of product characteristics (SmPC).

4.2.2.3 Rivaroxaban

4.2.2.3.1 Dose and administration [23, 24]

Day 1 to 21	Day 22 to 180	Day 181 onwards
15mg BD	20mg OD	20mg OD [a]

[a] The licensed dose of rivaroxaban in patients who required extended anticoagulation for long term prevention of VTE is 10 or 20mg OD. However, it should be noted that at the time of writing, only the 20mg dose has been studied specifically in people with cancer requiring extended anticoagulation via the SELECT-D study [24].

Renal Function (CrCl)	Dose
≥50ml/min	Use standard dose regime
<50ml/min but ≥ 15ml/min	Consider 15mg dose in patients who are deemed to have a higher bleeding risk than VTE risk.
<15ml/min	Contraindicated

Rivaroxaban must be taken with food.

Rivaroxaban is only available in a solid oral dosing form (tablets) for adult usage (granule formulations are only licensed in paediatrics).

In those who have difficulty swallowing, these tablets can be crushed and mixed with water or apple puree immediately before, and followed by food immediately after, ingestion.

There are no theoretical stability concerns around rivaroxaban being stored in a compliance aid.

4.2.2.3.2 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Active clinically significant bleeding.
- Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulants.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- Pregnancy and breast feeding.

4.2.2.3.3 Monitoring

See apixaban section 4.2.2.1.3.

4.2.2.3.4 Interactions

Concomitant therapies which have strong inhibitory / induction effects on both P-gp and CYP3A4 are generally contraindicated with rivaroxaban [23].

Therapies that either have strong effects on one of these systems or have a moderate effect on both of these systems are generally cautioned with rivaroxaban.

For further information consult the product summary of product characteristics (SmPC).

4.3 Summary of Main Points

- An individualised, risk-adapted approach must be taken when managing CAT.
- Treatment for CAT can be with either LMWH or a DOAC.
- Trials have suggested that LMWH is superior to warfarin / VKAs and that DOACs are non-inferior to LMWH.
- Most anticoagulants are off label for the treatment of DVT or PE in patients with active cancer.
- NICE recommends that PWC with confirmed DVT or PE should be offered anticoagulation treatment for 3 to 6 months. This should be reviewed at 3 or 6 months based on clinical need.
- It is good practice to determine the length of treatment on a case-by-case basis.
- When choosing anticoagulation treatment for CAT, consider the tumour site, interactions with other drugs including those used to treat the cancer and the risk of bleeding.
- Evidence suggests a higher rate of GI and genitourinary bleeds with a DOAC compared with LMWH. DOACs may be unsuitable for patients with tumours that are associated with an increased risk of these types of bleeds.
- The SSC recommends LMWHs for PWC with an acute diagnosis of VTE and a high risk of bleeding.
- DOACs are suggested for PWC with an acute diagnosis of VTE, low risk of bleeding and no drug-drug interactions with current systemic therapy.

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5.0 Important Considerations

In 2022, Musgrave *et al.* [1] published consensus recommendations for treatment of VTE in PWC including an algorithm to guide decision making when choosing anticoagulant therapy. The recommendations contain guidance on:

- Patients with GI impairment
- Patients with impaired renal function
- Patients with impaired liver function
- Patients at increased risk of bleeding
- Patients at risk of drug-drug interactions
- Patients with very high or low body weight and CAT
- Extended duration of anticoagulation beyond 6 months
- Management of recurrent VTE

You are advised to refer to this publication for in depth information on each of these important considerations. Some of these are briefly summarised below.

5.1 Patient Preference

Considering 'quality of life' for each person with cancer and discussing their personal preferences for anticoagulation is essential in choosing appropriate CAT therapy.

The importance of discussing the choice of anticoagulant with the patient cannot be over-empathised. Patients may have pre-conceived notions about their treatment based on previous personal experience or a family member/friends experience. It is important to address patients concerns in order to choose the anticoagulant best-suited for each patient. This should help increase compliance.

Studies have shown that patients with CAT tend to see themselves as a cancer patient first and a CAT patient second with their main concern centred around the impact that anticoagulation may have on their current cancer treatment [2]. Additionally, patients express concerns about safety, efficacy and ease of administration. Out of 100 patients, the most valued attributes were an anticoagulant with minimal interference with their cancer treatment (39%), low thrombosis recurrence rate (24%), and low risk of major bleeding (19%) [2].

In a qualitative sub-study of the Select-D trial using semi-structured interviews (n=37), most patients stated that tablets were more convenient, but injections were accepted in the context of having cancer [3].

The COSIMO study [4] asked patients to decide between hypothetical treatment options based on a combination of the following attributes: route of administration (injection/tablet), frequency of intake (once/twice daily), need for regular controls of the INR at least every 3 to 4 weeks (yes/no), interactions with food/alcohol (yes/no) and distance to treating physician (1 vs. 20 km). Patients strongly preferred oral

administration compared with self-injections, placing this of most importance when guiding treatment decision (73.8%). Order of importance of the other attributes were a regimen that did not include dietary restrictions, closeness to physician and once-daily dosing compared with twice-daily intake (11.8%, 7.2% and 6.5%, respectively) [4].

Crucially, it should be recognised that when making decisions about anticoagulant treatment patients may decide on a 'less-than-perfect' approach from a clinical perspective, but this is acceptable as long as they are aware of the risk/benefit ratio of their decision.

5.2 Increased Risk of Bleeding

Major bleeding: The ISTH define major bleeding in non-surgical patients as having a symptomatic presentation and 1:

- Fatal bleeding, and/or
- Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in haemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more or leading to transfusion of two or more units of whole blood or red cells.

Clinically relevant non-major bleeding (CRNMB): The SSC subcommittee on Control of Anticoagulation define CRNMB [5] as:

- Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
  - Requiring medical intervention by a healthcare professional
  - Leading to hospitalisation or increased level of care
  - Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Minor Bleeding: All reported bleedings not classified as major or CRNMB.

The presence of cancer roughly doubles the risk of bleeding and major bleeds in patients anticoagulated for a VTE [6]. The relative risks of bleeding with different anticoagulants varies according to patient characteristics such as age, renal impairment, prior history of bleeding and age.

LMWH trials in CAT patients showed no significant differences in major bleeding [7] and in the CLOT trial which used reduced dose LMWH after 4 weeks, efficacy was maintained compared to warfarin [8].

DOACs have been proven to be noninferior to LMWH in CAT, although some identified increased bleeding in patients with GI and GU malignancy compared to LMWH, or excluded some patients with specific cancers such as primary brain tumours (see Chapter 4).

Recommendations [1]

1. Patients with no absolute bleeding risk contraindication should be fully anticoagulated. An anti-Xa DOAC is the preferred option.
2. For patients with GIT or GU malignancy that is still *in situ,* the preferred anticoagulant is LMWH.
3. For CAT patients with an absolute bleeding contraindication (e.g., presence of active bleeding) and high thrombotic risk (such as a new VTE event in the preceding 4 weeks), consider the use of a retrievable IVC filter.
4. Resumption of anticoagulation and removal of the retrievable IVC filter once the bleeding resolves is recommended.

5.3 Drug-drug Interactions

It is important to consider the impact of drug-drug interactions. There is limited evidence on the effect of anti-cancer agents on DOACs. Information is largely theoretical. Potential interactions may occur particularly with drugs which are either inhibitors (e.g. crizotinib, lapatinib) or inducers of CYP3A4 and/or P-gp. These anti-cancer agents may theoretically effect plasma concentrations of DOACs and LMWH may be more appropriate.

5.4 Extremes of Body Weight

Consider LMWH in patients with BMI >40 kg/m^2 or weight >120 kg.

In addition to extremes of body weight other factors to be aware of when choosing anticoagulation that are related to weight and drug absorption include nausea, vomiting, GI surgery, GI absorption disorders and pre-existing conditions.

5.5 Anticoagulant Therapy Beyond Six Months

Evidence and clear consensus on how to manage anticoagulation beyond the six-month point is currently lacking, but the consensus is:

- Continue anticoagulation if patient still has active cancer (especially if metastatic disease and/or receiving SACT);
- Decisions should be made on an individual patient-to-patient basis, taking into consideration factors such as risk of recurrence, bleeding, interactions, patient's preference for oral or parenteral drug administration, and wishes.

Observational studies have been undertaken for dalteparin (the DALTECAN study), and tinzaparin (the TiCAT study) for patients requiring extended anticoagulation up to 12 months [9, 10]. Both studies showed no increase in bleeding rates or increases in recurrence rates with longer-term use. The Hokusai-VTE Cancer study (edoxaban) evaluated patient outcomes up to 12 months post-diagnosis [11]. However, a significant increase in major bleeding, especially in patients with GI or urological cancers, was observed.

Most guidelines recommend continuing with LMWH therapy if anticoagulant therapy is to continue beyond the six-month point; however, oral options can be considered if patients are unable to tolerate LMWH [12-14]. Reduced intensity anticoagulation may be appropriate beyond 6 months (e.g. apixaban 2.5mg BD or rivaroxaban 10mg OD).

In some cases, such as when a patient has a distal DVT or a peripherally inserted catheter (PICC) line associated DVT, 3 months anticoagulant therapy may be more appropriate than 6 months. If the line remains in situ the patient should be anticoagulated for at least 3 months and/or until line removal. If the line is removed the patient should be anticoagulated for at least 6 weeks.

5.6 Patients Receiving End-of-Life Care

Although many patients may benefit from continued anticoagulation after 6 months, the benefit may not be as clear for those receiving end-of-life care. In end-of-life care the assurance of the best possible quality of life should be the highest priority, thus thromboprophylaxis may eliminate the symptom burden related to CAT. However, randomised studies determining the benefits and risks profiles of prophylaxis in patients nearing the end of life are lacking [15].

The HIDDEN Study found that in 273 patients with advanced cancer admitted to palliative care units, approximately a third had a femoral DVT [16]. The DVT was not associated with thromboprophylaxis, survival, serum albumin concentration or symptoms other than leg oedema. Thromboprophylaxis might therefore confer no benefit over analgesia or other appropriate control measures for DVT symptoms in end-of-life PWC.

NICE recommend prophylaxis should be considered for patients receiving palliative care. However, factors including temporary increases in thrombotic risk factors, risk of bleeding, estimated life expectancy and the views of the patient and their family members or carers should be considered. NICE recommends LMWH as a first-line agent and fondaparinux in case of contraindications to LMWH [17].

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6.0 Common Complications

PWC with CAT have an increased risk of complications including bleeding (2-3 fold increase), recurrent VTE (2-6 fold increase) and death (6 fold increase) [1-3].

6.1 PICC-line / CVC Associated Thrombosis

PWC will often require a central venous catheter (CVC) for intravenous administration of chemotherapy and supportive therapies.

Apart from infections, the main complication of CVCs is thrombosis. The thrombus can form within, surrounding, or at the tip of the catheter. This can impair the flow in and out of the catheter. A CVC related thrombus refers specifically to a DVT that partially or fully blocks the vein in which the catheter sits.

A PICC is a type of CVC inserted via peripheral veins, usually in the arm. The risk of PICC line associated VTE is higher when compared to other CVC types [4-6]. There is evidence that the period of greatest risk is within the first 30-40 days post-insertion [7-11]. Local data from Hull, UK from 490 patients referred for PICC insertion (2012-2014) indicates an incidence of 6% PICC line associate VTE, in line with existing literature [12].

At present, thromboprophylaxis to prevent these events has not been proven effective, despite a number of RCTs.

A Cochrane review evaluated the efficacy of oral and parenteral anticoagulants in the prevention of CVC-related thrombosis and found no associated reduction in risk with either warfarin or prophylactic dose LMWH [13]. Therefore, the routine use of anticoagulants at prophylactic or therapeutic dose to prevent catheter-related thrombosis in patients with cancer is not recommended [14].

In PWC the preferred treatment of a CVC related thrombosis is anticoagulation without CVC removal. This should be possible as long as the catheter is correctly positioned. This is because re-insertion of the catheter can potentially expose the patient to further thrombosis and incur unnecessary delays in cancer treatment.

The CVC should be removed if it is no longer needed, if anticoagulation is contraindicated, if the CVC has become infected or if there is a failure to respond to anticoagulant treatment.

Decision making on choice of anticoagulant is the same as any other CAT. However, note there is no specific trial information on use of DOACs in patients with CVC line DVT.

6.2 Recurrent VTE

Patients with CAT are at an increased risk of VTE recurrence (9.6 per 100 patient years), with the greatest risk of recurrence in the first few months following diagnosis [15-16]. Patients with cancer have a 3-fold increased recurrence risk compared with non-cancer patients, and a higher rate of readmission to hospital because of VTE recurrence within six months of diagnosis [17].

Post-hoc analysis of the Hokusai VTE Cancer study showed that worse performance status (Eastern Cooperative Oncology Group score) was associated with VTE recurrence and major bleeding [18].

The CLOT study reported a VTE recurrence rate of between 6% and 9% [19]. In cases of recurrence or extension, BSH guidelines recommendations are summarised below (Table 5) [20-21].

Table 5
Summary of British Society for Haematology Recommendations for VTE Recurrence or Extension

Anticoagulant at the time of recurrence or extension	BSH recommendation
Warfarin	Switch to LMWH
Reduced dose LWMH	Switch to full-dose LMWH
Full-dose LMWH	Increase dose by 20-25%, guided by anti-Xa monitory. Target peak anti-Xa (4 hours post-dose) 1.6 - 2.0 u/ml OD or 0.8 - 1.0 u/ml for BD regimens. There is limited data to show that BD regimes are less likely to see recurrences. Example regimen: enoxaparin 1mg/kg.
DOACs	No evidence to guide management at present.

When considering switching medication you should first assess compliance, ensure correct dose and assess any possible interacting medication.

If recurrence occurs while on LMWH, rule out heparin induced thrombocytopenia (HIT).

A temporary IVC filter should only be inserted when there is a strong contraindication to anticoagulation and should be removed, if possible, as soon as anticoagulation is possible.

6.3 Incidental VTE

The increased use of highly sensitive, spiral, multi-slice CT in the diagnosis, staging and assessment of treatment response has led to an increase in the prevalence of incidental pulmonary embolism (IPE) in PWC [22-23]. The incidence of IPE in PWC (affecting both new and existing cases) ranges from 1% to 5% [23-24], depending on patient, treatment and cancer-related risk factors. Less commonly, DVT may be picked up incidentally on a staging/monitoring CT scan.

In general these should be treated as per patients with symptomatic DVT or PE.

The exception to this is incidental, asymptomatic, sub-segmental PEs (SSPE). To date, there have been no RCTs to assess how incidental SSPEs, in the absence of DVT, should be managed in the cancer population. These cases would tend to be treated with conventional approaches in PWC with the cancer present or still on active treatment. If anticoagulation is considered to be withheld due to, for example, concerns over high bleeding risk, bilateral leg dopplers would be recommended to exclude DVT. An initiation of a close clinical follow up is a possibility in the absence of DVT [25].

6.4 Thrombocytopenia

The presence of thrombocytopenia is an important risk factor for bleeding in patients being anticoagulated and so demands reassessment of the risk-benefit balance of anticoagulation. Post-hoc analysis of a RCT in CAT showed that thrombocytopenia (<100,000/µL) was associated with a 2 fold increased risk of major bleeding [26].

The European Haematology Association (EHA) [27] advises a general approach to anticoagulation for all cancer patients with thrombocytopenia:

- To reassess the indication of anticoagulation, irrespective of thrombocytopenia.
- To assess the ongoing associated thrombotic and bleeding risks resulting from generic and cancer-specific factors.
- To anticipate the duration of grade 3 – 4 thrombocytopenia.
- To formulate a clear anticoagulant management plan, to be reassessed frequently according to the individual treatment plan, kinetics of thrombocytopenia and possible complications or comorbidities.
- To consider restarting anticoagulant therapy, once the platelet count is consistently above a threshold deemed suitable for full anticoagulant dose and regimen.

The risk of patients with cancer developing thrombocytopenia within the first 3 months of anticoagulant therapy is high, especially patients with haematological malignancies

and those receiving regimens based on platinum, gemcitabine and anthracyclines [28].

Table 6 Recommendations for the Treatment of Thrombocytopenia	
Platelet Count	**Anticoagulation**
≥ 50 x 10^9 /L	Full dose LMWH / DOAC
< 50 x 10^9 /L	Consider platelet transfusion and use therapeutic LMWH / DOAC, especially in first month after VTE.
20 - 50 x 10^9 /L (if cannot maintain platelet count > 50 x 10^9 /L)	50% dose or prophylactic LMWH (or consider dose reduced DOAC).
< 20 x 10^9 /L	Withhold LMWH / DOAC, consider retrievable filter.
N.B. Excludes heparin induced thrombocytopenia (HIT) The table is an example of dosing guidance related to thrombocytopenia according to the EHA guidelines [27]. Some organisations may follow other guidelines such as those published by the BSH. Healthcare professionals are advised to check which guidance is in place at their individual organisations.	

6.5 Post-thrombotic Syndrome

Post-thrombotic syndrome (PTS), also known as post-phlebitic syndrome, is a complication of DVT. If a DVT damages the deep veins of the leg the increased pressure on the vein walls results in damage to the valves which normally work to keep blood flowing up the leg. This can lead to blood pooling in the foot and lower leg leading to pain, swelling, reduced movement and leg ulcers.

- Up to 30% of patients who have had a DVT will develop PTS symptoms within 5 years
- Most PTS episodes will develop within 6 months to 2 years of the initial thrombosis
- Patients who have had >1 episode of DVT in the same leg are at a higher risk of developing PTS
- Less commonly, PTS can develop in the limbs of the upper body if a patient has had an upper-limb DVT

Treatments for PTS usually include physical treatments such as compression stockings and leg elevation and over-the-counter analgesics. Studies on the use of other medications for the treatment of PTS have not shown any benefit.

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7.0 Further Training

Shared decision making, NICE guideline [NG197]:

https://www.nice.org.uk/guidance/ng197/resources/shared-decision-making-learning-package-9142488109

VTE prevention eLearning course, NHS:

https://www.e-lfh.org.uk/programmes/venous-thromboembolism-public-access/

Cancer associated thrombosis course, ISTH Academy:

https://academy.isth.org/isth/2019/cancer-associated-thrombosis/286356/faculty.presenter28s29.cancer.associated.thrombosis.html?f=c_id%3D286356%2Afeatured%3D16626&program=1

8.0 Notes