Thrombosis Clinical Guidelines

Cancer Associated Thrombosis (CAT)

GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Bae Abertawe Swansea Bay University Health Board

Contents

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1. Background

Cancer associated thrombosis, or CAT, is an overlooked area of oncology medicine. It is estimated that up to 1 in 5 cancer sufferers will have a thrombotic event during their cancer journey (1). CAT has been established as the second most common cause of death in cancer patients, behind the disease itself (2). Patients who develop CAT have been found to have lower survival rates, with studies showing a 12% one year survival rate for patients diagnosed with CAT vs 36% in control patients (3). CAT is more prevalent in the period immediately post cancer diagnosis (4). The risk of CAT is patient and disease specific, however many cancer therapies are known to increase the risk of developing CAT by up to six times. The risk of recurrent thrombo-embolic disease is increased two fold (5). The annual incidence of CAT for a patient receiving chemotherapy is 10.9% (5).

2. Risk Factors

CAT pathophysiology is often multifactorial, with some risk factors being common to non-cancer associated thromboses. Risk factors for the development of CAT are summarised below (6):

Patient Characteristics	Tumour Related Factors	Treatment Related Factors	Biomarkers
Female Gender	Anatomical site of tumour (see below)	Major surgery	High TF expression by tumour cells
Older Age	Tumour histology	Hospitalisation	Pre-chemotherapy platelets of >350 x 10^9/L
BAME Ethnicity	Advanced stage of cancer	Cancer Therapy	Pre-chemotherapy leucocyte count of >11 x 10^9/L
Other comorbidities (E.g. diabetes, obesity, decreased mobility?)	Initial period after diagnosis of cancer	EPO/GCSF	Elevated D-Dimer
Inherited Thrombophilia's		Central Venous Catheters	Soluble P-selectin, C-reactive protein

Table 1

Systemic Anti-Cancer Therapies (SACT) associated with higher risks of thrombosis include cisplatin, 5-fluorouracil, L-asparginase, tamoxifen, VEGF inhibitors (e.g. bevacizumab, sunitinib), lenalidomide, thalidomide, pomalidomide, and high dose steroids (e.g. dexamethasone) (6)

The Khorana Score (Table 2) is a tool used to estimate the risk of developing CAT in cancer patients receiving SACT (7). It classes patients with stomach or pancreatic cancer as being very high risk of developing CAT, and lung, lymphoma, gynaecological, testicular, and bladder being classed as high risk.

Thrombosis and Anticoagulation Clinical Guideline- Management of Cancer Associated Thrombosis

Patient Characteristic	Risk Score
Site of Cancer Very High Risk (Stomach or Pancreas)	2
Site of Cancer High Risk (Lung, Lymphoma, Gynaecological, Testicular, and Bladder)	1
Pre-chemotherapeutic platelet count ≥350 × 10^9/l	1
Haemoglobin concentration <100 g/l or use of erythropoiesis-stimulating agents	1
Pre-chemotherapeutic leucocyte count >11 × 10^9/l	1
Body mass index ≥ 35 kg/m^2	1
Thrombosis Rate per 2.5 months (%)- Based upon cumulative score from above	
Low Score (0)	0.3 - 0.8
Intermediate Score (1-2)	1.8 - 2
High Score (>2)	6.7 – 7.1

Table 2

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3. Prevention/Prophylaxis

3.1. Inpatient

Prevention of CAT is a complex subject area, with an emerging base of evidence. Studies have shown thromboprophylaxis strategies to be effective in preventing VTE, but have little impact on mortality (8). Guidelines support the use of thromboprophylaxis in all medical or surgical inpatients, and this also applies to cancer patients (9)

i) Patient with active or recent cancer, who have been admitted to hospital, should receive thromboprophylaxis throughout their admission, unless contraindicated (9,10)

ii) Cancer patients who undergo abdominal or pelvic surgery should be considered for extended thromboprophylaxis (9).

- NICE recommends LMWH for a duration of 28 days (11)

Thromboprophylaxis assessment should be undertaken for all inpatients as per the health board policy

3.2. Outpatient/Ambulatory

Data has shown that routine thromboprophylaxis in unselected cancer patient's results in increased bleeding risk, with unclear benefits. Therefore, routine thromboprophylaxis in ambulatory patients is currently not supported in any national or international guidelines. with the exception of the following two distinct clinical scenarios:

1) Patients who have myeloma and a receiving SACT with thalidomide, pomalidomide, or lenalidomide, with steroids (unless there is a contraindication). This should be with LMWH or 75-150mg of aspirin (9)

- Small observational studies evaluating the use of apixaban as thromboprophylaxis in this setting, but has yet to be validated using larger, controlled studies. Therefore, no national or international guidelines support the routine use of thromboprophylaxis in this setting at the time of writing

2) Consideration of thromboprophylaxis for ambulatory chemotherapy patients with high thrombotic risk (defined as a pre-chemotherapy Khorana score of 2 or greater). This should be with LMWH, rivaroxaban or apixaban. However consideration should be given towards the benefits vs harms of treatment, including bleeding risk, potential interactions (9,10,12)

- NICE guidelines recommend consideration of thromboprophylaxis in ambulatory SACT patients with pancreatic cancer, however as these patients would automatically have a Khorana score of at least 2, they are discussed as part of the above recommendations (11).

- Studies (including a Cochrane review (13)) have shown that ambulatory

thromboprophylaxis in high thrombotic risk cancer patients receiving chemotherapy is associated with a decreased risk of thrombotic events, but an increased risk of bleeding, and no overall benefit in terms of survival. Therefore the practice cannot be recommended as a standard of care for these patients at this time. Patients should be individually assessed, and the merits of anticoagulation discussed with patients. Following two recently published clinical trials (AVERT (14) and CASSINI (15)), there is now data to support the use of rivaroxaban and apixaban as prophylactic anticoagulants in this setting.

- It should be noted however that this recommendation does not apply to patients with acute leukaemia, myeloproliferative neoplasm, planned stem cell transplantation, history of cancer in remission, on hormonal therapy alone, hospitalized, or post-surgery

Although central venous catheters are associated with a high prevalence of VTE, guidelines do not support the routine use of thromboprophylaxis in ambulatory patients (9,16)

- The use of thromboprophylaxis may be considered on a case by case basis under the specialist advice of the patient's oncologist.
- ISTH recommends that catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium in order to reduce the risk of catheter associated thrombosis (16)

3.3. Thromboprophylaxis Therapeutic Options

It should be noted that all therapeutic options listed below are unlicensed in the setting of ambulatory thromboprophylaxis of cancer patients

i) Enoxaparin 40mg OD

ii) Apixaban 2.5mg BD

iii) Rivaroxaban 10mg OD

iv) Aspirin 75-150mg OD (multiple myeloma patients only)

3.4. Patient Factors

All cancer patients should be educated on the risks of CAT and measures that they can take to reduce the risk. Patients should be advised on general measures such as staying active, maintaining good hydration, and stopping smoking.

Patient information resources should be made available within the waiting areas of the oncology and haematology department. The website CancerClot™ has been developed in partnership with Leo Pharma, and is an interactive resource that can be used to inform patients of the risks of thrombosis.

4. Diagnosis

CAT can be broadly divided into two areas;

- Symptomatic VTE where the patient presents with symptoms indicative of a VTE.
- Incidental VTE whereby the VTE is identified usually as a result of a separate diagnostic process.

4.1. Symptomatic VTE

Diagnosis should be as per local and national guidelines for medical DVT and PE patients. The use of D-Dimer in cancer patients is controversial, given that D-Dimer levels are expected to be higher in cancer patients (17). Small studies have shown D-Dimer to be a safe method of excluding DVT and PE (17), however data also shows that 88-94% of cancer patients require further diagnostic evaluation beyond WELLS scoring and D-dimer analysis, negating the values of D-dimer testing in this patient group.

4.2. Incidental VTE

Patients who are diagnosed with incidental CAT should be managed in the same way as those who are diagnosed with symptomatic CAT (9,10).

This is with the exception of incidentally diagnosed visceral vein thromboses, in which anticoagulation should be considered on a case by case basis (10)

- This is due to unclear evidence in terms of harm caused by the thrombus, and benefit of anticoagulation. Most practice is currently based on clinician's opinion and anecdotal experience.

4.3. Patient Factors

A recent study by Professor Simon Noble, the PELICAN study, highlighted high anxiety rates amongst patients diagnosed with CAT, and a lack of adequate support networks (18).

Since summer 2017, a CAT pathway for ambulatory patients has been running in Singleton's Acute GP Unit Pharmacy-led VTE Clinic, and at Neath Port Talbot Hospital since 2019.

New CAT diagnoses are referred to the service, following a medical assessment of the patient's suitability for ambulatory management, by completing the following referral from, and contacting;

- **For Swansea patients:** The acute GP unit on ext 38660
- **For Neath patients: Contact** ext 42171

The service will ensure ongoing supply and review of the medication. The service also offers support and information provision to patients

If the patient cannot be referred to the service, the website CancerClot™ can be used as a patient information resource, containing videos, articles, etc. Booklets and leaflets are also available from pharmacy.

5. Management

5.1. Aim of Treatment

The aim of initial anticoagulant therapy in Cancer Associated Thrombosis is:

- To prevent fatal PE
- To prevent recurrent VTE
- To prevent long term VTE complications (e.g. Post-Thrombotic Syndrome)

5.2. Pre-Treatment Monitoring

Prior to initiating anticoagulation, the following parameters should be monitored:

- Urea and Electrolytes
- Full Blood Count
- Liver Function Tests
- Coagulation Screen

Below, are common monitoring parameters and guidance on what to do if these are out of range. This is not an exhaustive list, and blood results should be assessed in full.

Test	Reference	What to do if outside of normal range?
Creatinine Clearance (CrCl)	Tinzaparin: >20ml/min	Use standard dose
	Tinzaparin: <20ml/min	Use standard dose. Monitor anti-Xa level after 4 hours post 3rd-4th dose. Discuss with haematology if levels outside of accepted ranges
	DOACS: Check product SmPC	**No DOAC is licensed at a CrCl of <15ml/min** Consider alternative therapy
Platelets	DOAC/LMHW: >50x10^9/L	Continue with full dose (especially if within the first 3 months of therapy) - Close monitoring indicated
	DOAC: <50x10^9/L	Avoid usage
	LMWH: 25-50x10^9/L	**If High Risk Thrombotic Extension:** Platelet transfusion to achieve platelet counts ≥40-

		50x10^9/L and then give full dose LMWH (19). **If Low Risk Thrombotic Extension:** Use 50% of LMWH dose or prophylactic dose if high bleeding risk (19)
	LMWH: <25X10^9/L	Do not initiate anticoagulation. Discuss with haematology
LFT's	LMWH	No restrictions listed in SmPC. LMWH's may, uncommonly, cause changes to LFT's.
	DOACs	Contraindicated in patients with hepatic disease and associated coagulopathy and clinically relevant bleeding risk. Cautioned in people with mild to moderate hepatic impairment
Haemoglobin (Hb)	LMWH and DOAC's	Clinical decision whether to initiate anticoagulation. Of note, DOAC's and LMWH are contraindicated in cases of active major haemorrhage or patients at high risk of major haemorrhage. Consult the relevant product SmPC.
Patient Body Weight	LMWH	Data for the use of LMWH in high body weight is currently lacking. Data is currently available for the use of enoxaparin up to 144Kg, tinzaparin up to 165Kg, and dalteparin up to 190Kg. **anti-Xa monitoring should be undertaken for patients outside of these weights.** A Cochrane review found no difference in outcomes (efficacy and safety) if the dose is given as a single once a day dose, or divided equally into two doses (20).
	DOAC's	ISTH does not recommend the use of DOAC's in patient weighing >120Kg, unless there is scope to undertake therapeutic drug monitoring (21)

5.3. Initial Therapy (First ONE Month)

First Line: Tinzaparin 175units/Kg subcutaneously ONCE each day

Second Line: Oral treatments (see below)

**** All therapies will need to be managed in secondary care****

5.4. Subsequent Therapy (Month TWO to SIX)

5.4.1. Treatment Options

- Although LMWH has been the cornerstone of anticoagulation in CAT for the past 17 years, the evidence for newer therapies, the DOAC's, has grown substantially in recent times
- *The rationale for oral therapies stems from the CLOT study (22), which demonstrated the benefit of 6 months of LMWH therapy over oral vitamin K antagonist (VKA) therapy.*
- However, evidence for the use of DOAC's has been published in recent years
- This is in the form of the HOKUSAI-VTE Cancer (edoxaban) (23), SELECT-D (24) (rivaroxaban) and CARAVVAGIO (apixaban) (25) studies.
- The HOKUSAI study highlighted a tendency towards better efficacy for edoxaban (compared to dalteparin), but with a significant risk of major bleeding (23). Subgroup analyses identified the greatest risk of bleeding to be in patients with luminal gastrointestinal cancers or urothelial cancers.
- The SELECT-D study identified similar findings (24)
- In response to this the ISTH published guidance, advocating the use of DOAC's (rivaroxaban and edoxaban) as first line therapies for CAT, with the exception of those patients with luminal GI or urothelial cancers (26).
- Since then further guidelines such as ASCO (10) and NICE (27) have advocated DOAC's as first line therapies
- The CARAVAGGIO study, comparing apixaban and dalteparin was published in 2020, and showed the non-inferiority of apixaban in terms of efficacy, with a similar bleeding profile (25).
- However, it should be noted that there is a lack of heterogeneity amongst studies, with only low number of upper GI cancer patients and no primary brain or intracerebellar metastases included in CARRAVAGIO
- It should also be noted that DOAC's have more drug-drug interactions, and less flexibility when it comes to obesity, thrombocytopenia, recurrence on anticoagulation, than LMWH
- DOAC's may also not be convenient in patients whereby absorption of oral therapies is compromised, e.g. severe nausea and vomiting, patients who have undergone GI surgery
- It is also worth noting that at present, no DOAC has a license specifically for CAT treatment
- Therefore this guidance advocates an algorithmic approach to management (see below)

** For guidance on initiation of DOAC's, please refer to the health board policy **

5.4.2. Treatment approach following one month of LMWH

Step 1: Can absorption of an oral agent be guaranteed?

- Patients with poor oral intake or sever nausea and vomiting should be placed on LMWH in preference to a DOAC
- The impact of GI surgery, for example ileostomy, colostomy, gastrectomy, should be considered in relation to absorption of DOAC's
  - ➢ DOAC absorption is primarily in the stomach, duodenum and proximal jejunum (28)

Step 2: Are there any clinically relevant drug interactions?

- DOAC's have more drug-drug interactions than LMWH
- Interactions between DOAC's and the patients SACT regime should be evaluated
- For guidance consult the product SmPC or the Liverpool Cancer Drug Interaction website/app.

Step 3: Are there any contraindications to a DOAC?

- DOAC's are NOT suitable in patients with platelet counts of $<50x10^9/L$
- DOAC's are NOT suitable in patients who have a recurrent VTE on anticoagulation
- DOAC's are not suitable for patients with a CrCl of <15ml/min
- DOAC's are not suitable for patients who weigh more than 120Kg or less than 50Kg

Step 4: What does the patient want

- Based upon the above, confirm with the patient if they would prefer oral or parenteral therapy

Step 5: What agent should be initiated?

- **Upper GI/genitourinary malignancy:** First Line: Tinzaparin 175units/Kg OD, Second Line: Apixaban (although there was low representation of UGI malignancy in the study)

  Colorectal malignancy: First line: Apixaban, Second Line: Tinzaparin 175units/Kg OD
- **Brain primary/metastases:** First Line: Tinzaparin 175units/Kg OD, Second Line: Edoxaban (although there was low representation of these patients in the study)
- **All other:** First line: Apixaban, edoxaban, rivaroxaban, Second Line: Tinzaparin 175units/Kg OD

5.4.3. DOAC Licensing in cancer

- It should be noted that DOAC's do not have a specific license for use in cancer associated thrombosis (CAT), however it is not clear as to whether this means that their use in cancer patients with VTE is unlicensed, or covered by the general VTE management license.
- Apixaban and edoxaban SmPC's have specific statements with regards to the lack of data in cancer patients, however this statement is not strictly speaking true since the publication of Hokusia-VTE Cancer and Caravaggio
- Rivaroxaban's SmPC does not contain such a statement
- However, it should also be noted that most CAT guideline published since 2018 advocate DOAC's as first line therapies, hence the rationale behind this guideline taking a similar approach

Key
Yes
No

osis and Anticoagulation Clinical Gu

CAT Management algorithm (after initial 30 day treatment)

Review regularly as situation develops

Can the absorption of oral medication be guaranteed in this patient?

No → Use tinzaparin 175units/Kg OD with patient or carer to administer

Yes

Are there ANY clinically relevant drug interactions with the patient's regular and oncological treatment and DOAC's

Yes → Use tinzaparin 175units/Kg OD with patient or carer to administer

No

Are there ANY contraindications to a DOAC, e.g.

- Platelets <50x10⁹/L
- VTE on anticoagulation
- CrCl <15ml/min
- Wt <50Kg or >120Kg

Yes → Use tinzaparin dosed as per CAT policy

No → Cancer type

- Upper GI / Genitourina → **First line:** Tinzaparin 175unit/Kg OD
  Second Line: Apixaban (*although clinicians should be aware that only small numbers of these patients were included in the study*)
- Colorectal → **First Line:** Apixaban
  Second Line: Tinzaparin 175unit/Kg OD
- Brain mets/ primary → **First Line** Tinzaparin 175 unit/Kg OD
  Second Line: Edoxaban (*although clinicians should be aware that only small numbers of these patients were included in the study*)
- All other → **First Line:** Apixaban, Edoxaban or Rivaroxaban
  Second Line: Tinzaparin 175unit/Kg OD

Author: KP, SJE Produced: April

N.B. DOAC's are currently unlicensed in CAT

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5.4.4. Upper Extremity DVT

The following additional guidance applies to Cancer Associated Upper Extremity DVT (29).

- **The American College of Chest Physicians (ACCP) recommend the upper extremity DVT involving the axillary or more proximal veins, have acute anticoagulation with LMWH (29)**
- **If the thrombosis is related to a central venous catheter (CVC) then it is recommended that the CVC is not removed if it remains functional, and there is an ongoing need for its use (29)**
- **If the CVC is removed, the recommended duration of anticoagulation is 3 months (29)**
- **If the CVC is not removed, then anticoagulation must be continued whilst the CVC is *in situ*, to a minimum of three moths (29)**

There is little evidence to support the use of DOAC's in upper extremity DVT

5.5. Post-Initiation Monitoring

5.5.1. Monitoring Schedule

This is for routine monitoring, and excludes any additional or more frequent monitoring indicated by the patients clinical condition.

LMWH	Re-check U+E, FBC on **day 6, 30,** and every **two months** thereafter
DOAC	Re-check U+E and FBC on **day 30,** then undertake monitoring as per the health board DOAC monitoring guideline

5.5.2. Monitoring Parameters

The parameters listed below are not an exhaustive list, and provide guidance on common complications of therapy

Creatinine Clearance (CrCl)	LMWH: <20ml/Min	Use standard dose. Monitor anti-Xa level after 4 hours post 3rd-4th dose. Discuss with haematology if levels outside of accepted rages
	DOACS: Check product SmPC	No DOAC is licensed at a CrCl of <15ml/min Consider alternative therapy
Platelets (PLTS)	LMHW: Decrease to	**If < 30 days since index event:** See above

	<50x10^9/L	**If > 30 days since index event:** *If PLTS 25 to 50x10^9/L:* Use 50% dose tinzaparin or prophylactic LMWH (subject to bleeding risk) *If PLTS <25x10^9/L:* Temporarily withhold
	LMWH: Decrease from baseline of 30% or more	Suspect heparin induced thrombocytopenia (HIT), especially if signs of rebound thrombosis or skin allergy. However, consideration should also be given to the fact that chemotherapy may also result in decreases in platelet levels. **If heparin induced thrombocytopenia is suspected, contact haematology**
Haemoglobin (Hb)	LMWH/DOAC: Fall of 20g/L	The SmPC (30) for tinzaparin defines a major bleed as being a fall in Hb of 20g/l or more. Changes in Hb should be investigated, and a clinical decision made as to whether to continue if a major bleed is identified. Alternative methods of anticoagulation may need to be considered. **Discuss with haematology if indicated**
Potassium (K+)	LMWH: >5.3mmol/L	Heparins may suppress secretion of aldosterone, thus increasing serum potassium levels. Patients are at a higher risk of hyperkalaemia if they have diabetes mellitus, chronic renal failure, raised baseline creatinine, or take medication that is known to increase potassium. More frequent monitoring may be indicated in these individuals. Hyperkalaemia is usually reversible on discontinuation of therapy.

5.6. Changing therapy within the first six months

Anticoagulation should not routine be changed within the first six months, unless the patient does not tolerate the initial therapy, or a change in the patients clinic picture makes the chosen treatment not appropriate

N.B. Patients who are classed, as being "cancer free" within the first six month of therapy should not have a change in their anticoagulant management for this reason alone.

5.7. Thrombosis re-occurrence during therapy

Thrombosis re-occurrence has been shown to occur in around 6-9% of CAT patients whilst using LMWH, and 10-17% of CAT patients whilst taking warfarin (31). Evidence on management strategies is currently lacking. BSH recommends the following (9):

- **If the patient is taking an oral anticoagulant, switch to LMWH**
- **If the patient is on therapeutic dose anticoagulation, consider one of the following strategies:**
  - **i) Increase the tinzaparin dose by 25%**
  - **ii) Switch to 1mg/Kg BD enoxaparin**
- **In both instances, peak anti-Xa levels should be monitored 4 hours post the 3rd or 4th dose :**
  - **i) Peak anti-Xa level of 1.6 – 2.0 units/ml for once daily LMWH**
  - **ii) Peak anti-Xa level of 0.8-1.0 units/ml for twice daily LMWH**
- **The use of IVC filters are generally not recommended, unless there is definitive contraindication to anticoagulation, in which case they should be used with a planned point to remove them once anticoagulation can be re-initiated. (9)**
- **If thrombosis extension occurs despite these interventions, discuss with haematology**

6. Management – Beyond 6 Months

6.4. Is your patient still at risk of thrombosis?

Evidence and clear consensus on how to manage anticoagulation beyond the six-month point is currently lacking. However the general consensus is:

- **Continue anticoagulation if cancer still active (especially if metastatic disease and/or receiving SACT)**
- **Consider continuing if index VTE event was a high volume thrombus**
- **Decisions should be made on an individual patient-to-patient basis, taking into consideration factors such as risk of re-occurrence, bleeding, interactions, and patient wishes.**

6.5. Patients taking tamoxifen

Danish registry data of women who have had breast cancer found those taking tamoxifen had a 5 year VTE incidence 1.2%, compared to 0.5% to those who were not (32). If a patient has had CAT, and will require longer term treatment with tamoxifen, anticoagulation may need to be extended for the period that the patient is taking tamoxifen (9). Aromatase inhibitors are associated with significantly lower VTE risks than tamoxifen (32).

6.6. Risk assessment for re-occurrence

No validated method of estimating risk of CAT re-occurrence is currently available. However, the Ottawa score may be used as a method of facilitating shared patient-clinician decision making (34)

Factor	Point
Female	1
Lung Cancer	1
Breast Cancer	-1
TNM Stage I	-2
Previous VTE	1
Interpretation	
Total Score	**Risk**
-3 to 0	Low
1 to 3	High

6.7. Therapeutic Options

Evidence for anticoagulant strategies beyond the initial six months is currently lacking. Observational LMWH studies have been undertaken for dalteparin (DALTECAN) (35) and tinzaparin (TICAT) (36) for patients requiring extended anticoagulation up to 12 months. Both studies showed no increase in bleeding rates or increases in re-occurrence rates with longer-term use. The Hokusai-VTE Cancer study (edoxaban) (23), evaluated patient outcomes up to 12 months post diagnosis. However, as discussed above, a significant increase in major bleeding, especially in patients with GI or urological cancers, was observed. Apixaban and rivaroxaban studies both terminated at the six month point (24)(25). As a general rule, the therapy used in the first six months can be continued if the patient is happy to do so. However, switches can be undertaken if the patient and clinician feel that it is appropriate to do so.

If the DOAC option is chosen, there is some debate around the most efficacious dose in cancer patient. As stated above most DOAC trials stopped at the six month point. Both rivaroxaban and apixaban have licensed dose reductions beyond the six month point in general VTE, however representation of active cancer patients within these studies were low. A recent study has shown the efficacy and safety of rivaroxaban at the 20mg dose when used beyond the six month point, hence it is recommended that this dose is used in preference to the 10mg dose (37). Apixaban is a little more complex. Only the 2,5mg dose is licensed beyond the six month point, however this comes from data showing a similar efficacy and safety between that dose and the standard 5mg dose, when used in patients whereby there is clinical equipoise whether to continue treatment beyond the six month point (38). Active cancer patients were excluded from this study, hence the data is unlikely to be representative of this population. The ApiCAT study, which evaluates the safety and efficacy of 2.5mg vs 5mg apixaban in cancer patients beyond the six month point, is due to be completed by 2023, hence we won't have meaningful data until that point. In the absence of rigid data, our recommendation is to follow the licensed dosing recommendation of 2.5mg BD when apixaban is used beyond the six month point.

First Line: Continue with treatment used during first six month period

If edoxaban is chosen, continue at the 60mg dose (unless dose reduction factors apply- see SmPC)

If rivaroxaban is chosen, continue at the 20mg dose (as renal function allows)

If apixaban is chosen continue at the 2.5 mg dose

LMWH patients can switch to oral if patient wishes, and oral therapy appropriate for patient

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