Nottingham University Hospitals NHS
NHS Trust

Guideline Number & Full Title:	3343 - Guideline for the management of cancer-associated venous thromboembolism (CAT).
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Scope ***(Target audience, state if Trust wide):***	Target audience is for haematologists, oncologists and those treating patients with cancer.
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Explicit definition of patient group to which it applies ***(e.g. inclusion and exclusion criteria, diagnosis):***	This guideline applies to patients with cancer who may require thromboprophylaxis against VTE or treatment for VTE.
Changes from previous version ***(not applicable if this is a new guideline, enter below if extensive):***	Not applicable
Summary of evidence base this guideline has been created from:	National and international guidelines as well as phase 3 clinical trials; please see references
This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust .	

Contents

Guideline for the management of cancer-associated venous thromboembolism (CAT).

1. Introduction

- Patients with cancer have a four-fold increased risk of venous thromboembolism (VTE) compared to those without cancer. Many factors affect this risk, including type of cancer, treatment, presence of central venous access device (CVAD) and background VTE risk factors.
- However, patients with cancer also have a two-fold increased risk of anticoagulant related bleeding and therefore choice of treatment for cancer-associated VTE needs to be carefully considered.

2. Primary thromboprophylaxis

- Risk factors for venous thrombosis (VTE) include tumour site, metastatic disease and treatment plan as well as general VTE risk factors for example, previous history of VTE, obesity or surgical intervention.
- Primary prophylaxis is **not** recommended in all ambulatory outpatients patients with cancer receiving systemic anticancer therapy. Occasionally this may be considered on an individual patient basis if thrombotic risk is felt to be particularly high and bleeding risk low. There is some evidence that the Khorana score may be helpful in these situations.

- Primary thromboprophylaxis **should be considered** in certain patient groups. In each case, this needs to be balanced with the risk of bleeding in the individual patient. These would include;
    - Patients undergoing cancer surgery should receive primary thromboprophylaxis post-operatively with low molecular weight heparin (LMWH) for 7-10 days, if not at high risk of bleeding.
    - Post-operative thromboprophylaxis with LMWH should be extended to 28 days following major abdominal or pelvic cancer surgery, provided that these patients are not at high risk of bleeding.
    - Primary thromboprophylaxis with LMWH is indicated in ambulatory patients with locally advanced or metastatic pancreatic cancer, being treated with chemotherapy who have a low bleeding risk.
    - Patients treated with medications which carry an additional risk of VTE (eg. tamoxifen or lenalidomide) should be risk assessed for primary thromboprophylaxis.

- Primary thromboprophyalxis **is not** indicated in patients with;
    - Locally advanced or metastatic lung cancer
    - Routinely for patients with central venous access devices (CVAD)
    - Patients with a high risk of bleeding
- Thromboprophylaxis in patients with the following conditions have less evidence to support them. The below advice is based on consensus opinion amongst the non-malignant haematology team.
    - Patients with a previous history of VTE; thromboprophylaxis should be considered in patients with a personal history of VTE who have active cancer and/or undergoing cancer treatment. This should be balanced against individual bleeding risk and should be regularly reviewed throughout their treatment, particularly towards the end of life.
    - High risk thrombophilias, such as antithrombin deficiency, protein C or protein S deficiency; these diagnoses should be taken into consideration when considering thromboprophylaxis in ambulatory patients but does not, in isolation, warrant thromboprophylaxis.
    - Low risk thrombophilias, such as factor V Leiden and prothrombin gene mutation; the additional VTE risk due to low risk thrombophilias is low and therefore thromboprophylaxis is not required unless there is a personal history of VTE.
    - First degree family history of thrombosis; the circumstances around the family history of VTE require consideration here. A first degree family history of unprovoked proximal DVT or PE carry a higher thrombotic risk for the patient, than a family history of provoked VTE or a VTE history in more distant relatives. Decisions need to be made on an individual patient basis.
    - Other VTE risk factors (such as BMI, smoker etc) may be considered when assessing thrombotic risk but should not be an indication for thromboprophylaxis on their own.
    - The decision to prescribe thromboprophyalxis should be reviewed regularly throughout treatment for cancer, especially if a decision for end of life care is made.

3. Treatment of CAT

Patients diagnosed with venous thrombosis (VTE) as an incidental finding on imaging, should be managed in the same way as those presenting with symptomatic VTE.

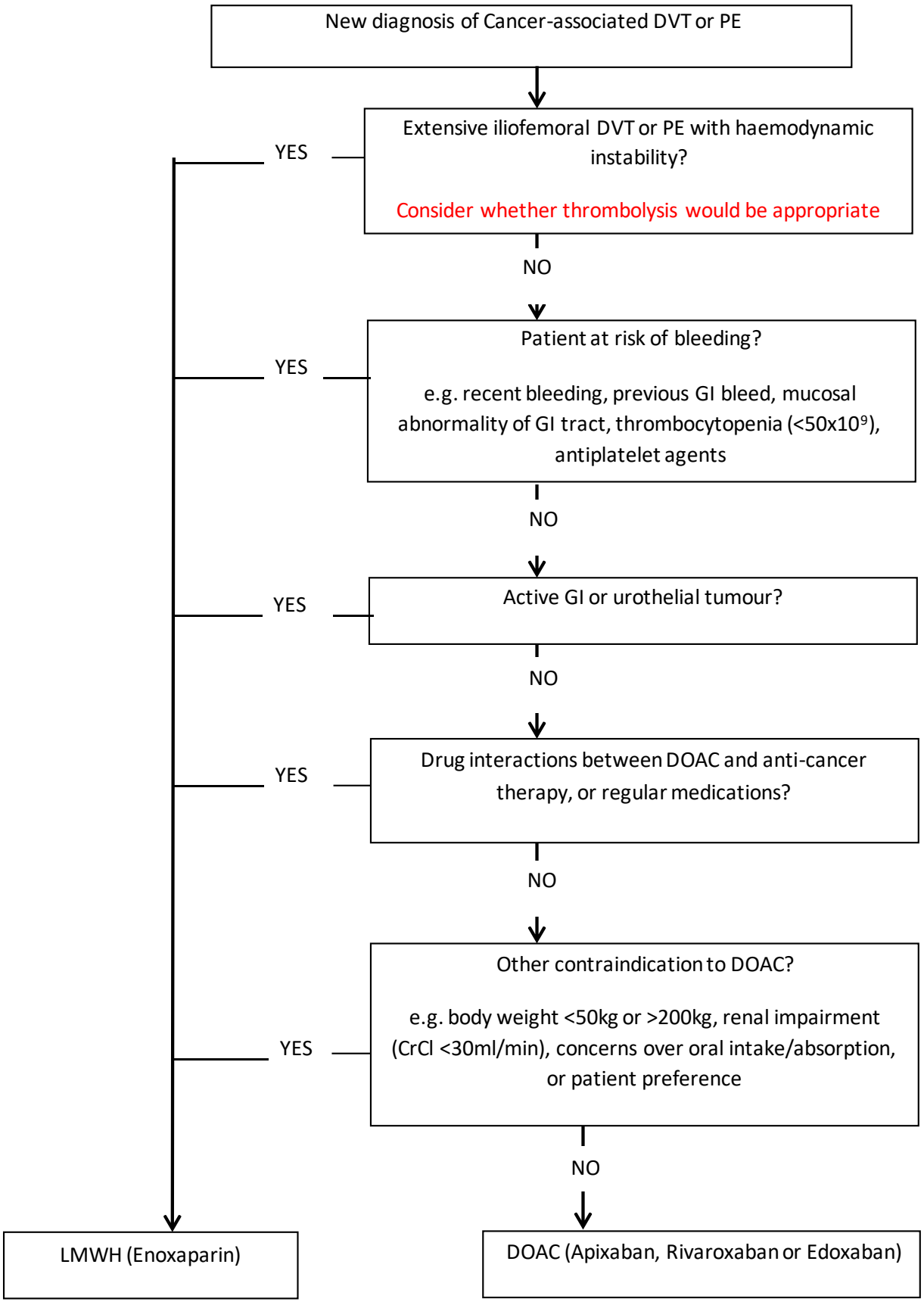
3.1 Drug choice

- Low molecular weight heparin (LMWH) has been the gold standard for treatment of cancer-associated VTE since the CLOT trial. This showed that LMWH was superior to warfarin in preventing recurrent VTE.
- There is now evidence for the use of the DOACs as an alternative to LMWH in treating cancer-associated VTE. Of note, all these trials excluded patients with an ECOG performance score of 3-4.
- Edoxaban (Hokusai VTE Cancer), Rivaroxaban (SELECT-D) and Apixaban (Caravaggio) have all been shown to be non-inferior to LMWH in preventing recurrent VTE in their respective clinical trials. However, major bleeding and clinically relevant non-major bleeding are higher

in the DOAC treatment arms than the LMWH arms for all. This difference was only statistically significant in the Hokusai-VTE Cancer and SELECT-D trials.

- Post-hoc analysis of these trials has suggested that the majority of the bleeding was gastrointestinal (GI) bleeding, and this was primarily observed in patients with cancer affecting the GI tract.
- As a result the International Society of Thrombosis and Haemostasis (ISTH) suggests ***LMWH as a preferential treatment*** for cancer associated VTE in patients with:
    - high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary,
    - cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes,
    - active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis.
- In other patient groups, both LMWH and DOAC are reasonable alternatives. Decisions regarding which drug to use should take into account potential drug interactions as well as patient preference.
- There are a number of important drug interactions between DOACs and other medications, including some of the systemic anti-cancer therapies. Further information about potential drug interactions can be accessed from a variety of sources (e.g. European Heart Rhythm Association; https://academic.oup.com/eurheartj/article/39/16/1330/4942493 or https://cancer-druginteractions.org/checker).

- *NB: Any patients diagnosed with DVT via the community-led/nurse-led DVT pathway in Nottingham, with a background of active malignancy, will be commenced on LMWH pending review by the Oncology team to establish whether a DOAC would be suitable option.*
    - *This decision should be reviewed in the oncology clinic and further advice sought from haematology if required.*


New diagnosis of Cancer-associated DVT or PE
Extensive iliofemoral DVT or PE with haemodynamic instability?
Consider whether thrombolysis would be appropriate
YES
NO
Patient at risk of bleeding?
e.g. recent bleeding, previous GI bleed, mucosal abnormality of GI tract, thrombocytopenia (<50x10⁹), antiplatelet agents
YES
NO
Active GI or urothelial tumour?
YES
NO
Drug interactions between DOAC and anti-cancer therapy, or regular medications?
YES
NO
Other contraindication to DOAC?
e.g. body weight <50kg or >200kg, renal impairment (CrCl <30ml/min), concerns over oral intake/absorption, or patient preference
YES
NO
LMWH (Enoxaparin)
DOAC (Apixaban, Rivaroxaban or Edoxaban)

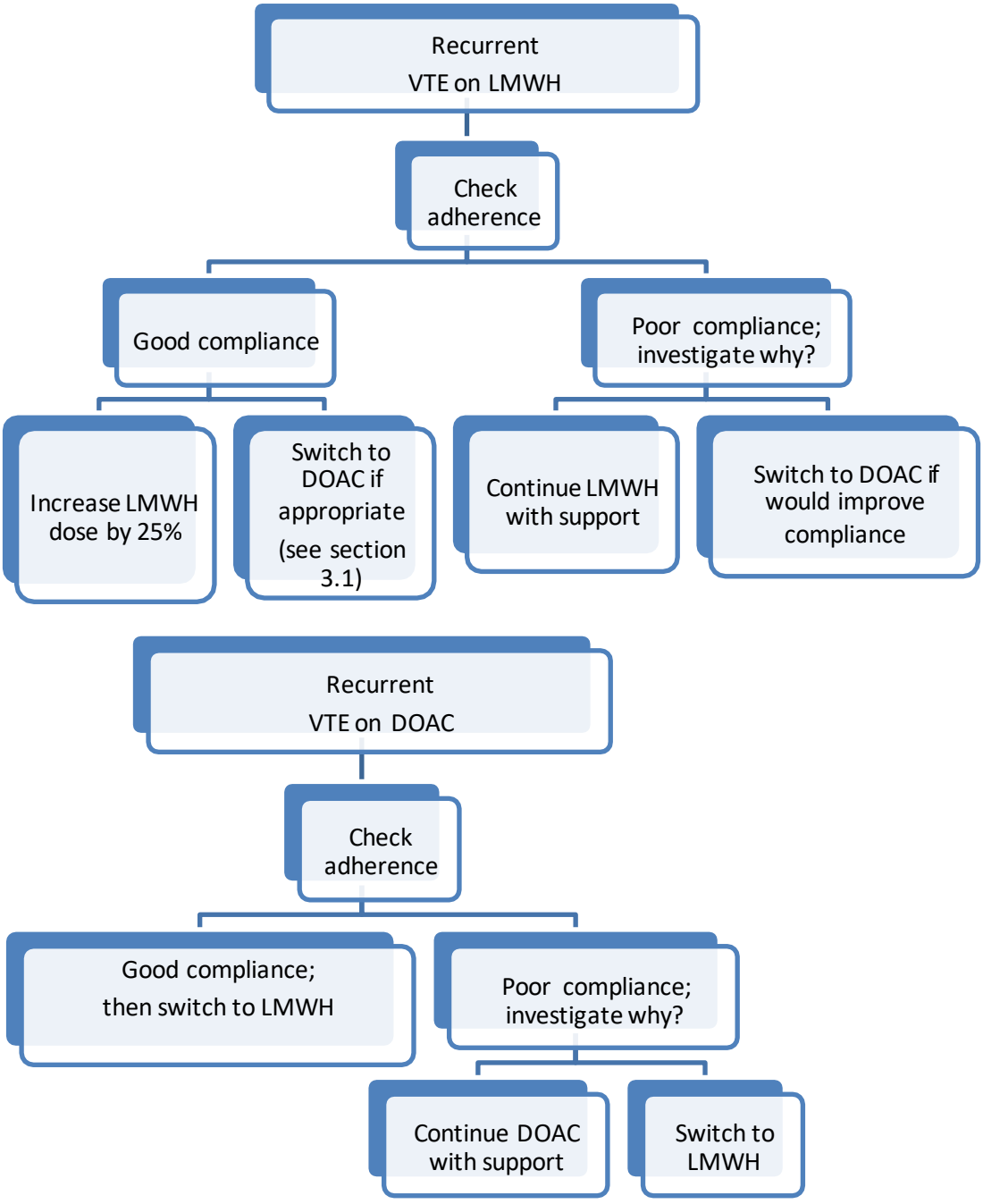
3.2 Duration

- Patients with cancer-associated VTE should receive anticoagulation for a minimum of 6 months.
- While there is a good evidence base for anticoagulation for the initial 6 months treatment, the evidence after this time point is less robust.
- If after 6 months, there is no evidence of active cancer **AND** the patient is not receiving any treatment with an associated risk of VTE (e.g. tamoxifen), then anticoagulation could be discontinued at that stage.
- Otherwise, anticoagulation ought to continue until such time that;
    - there is no longer evidence of active cancer,
    - the patient is no longer receiving any treatment with associated risk of VTE,
    - or the patient's risk of bleeding is deemed too high to continue anticoagulation.
- If continuing anticoagulation beyond 6 months, then there may be scope to alter the choice of anticoagulant depending on the circumstances, eg. converting to Apixaban 2.5mg BD if the only indication for ongoing anticoagulation is treatment with Tamoxifen. These decisions can be discussed with haematology on an individual patient basis if required.

4. Special circumstances

4.1 Recurrence

- Some patients with cancer who are already on anticoagulation with LMWH or DOAC will unfortunately develop recurrent VTE (4-9%).
- This is more common in patients with advanced cancer.
- When considering ongoing treatment following recurrence, review of current anticoagulation should be made.
- Points to consider include adherence, correct dose and is the patient taking their anticoagulation correctly (e.g. taking Rivaroxaban with food).
- There is no routine role for checking anti-Xa level.

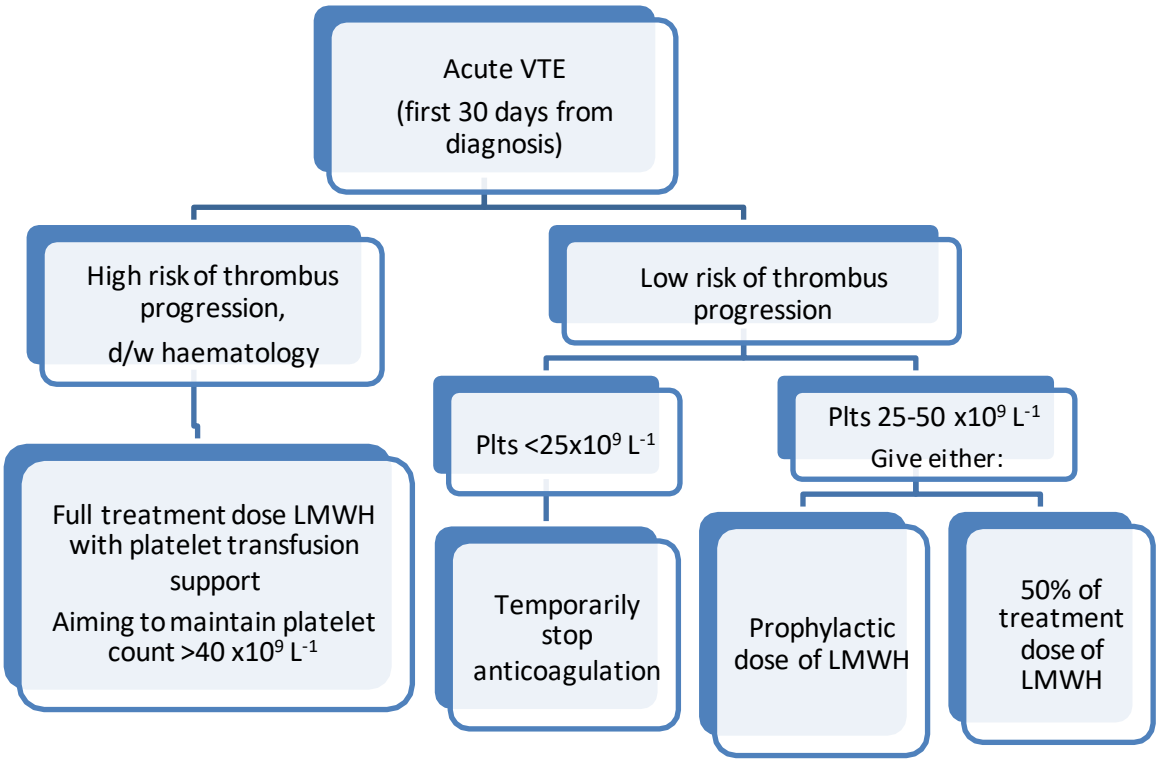


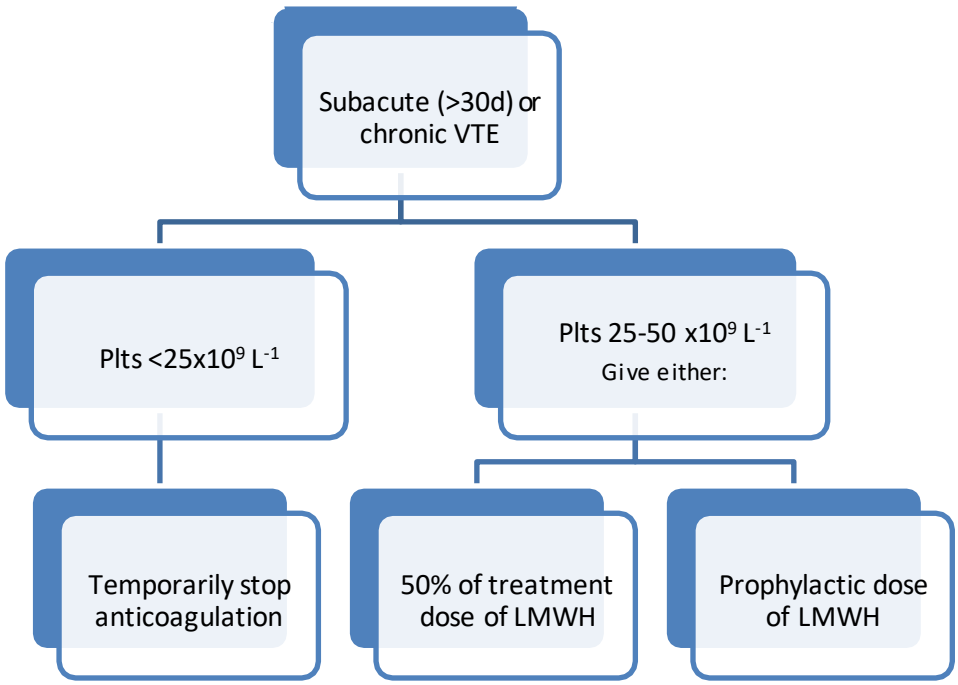
- If the LMWH dose is increased following recurrent VTE, consider a twice daily (BD) rather than once daily (OD) dosing schedule as higher doses of LMWH may be better delivered BD.
- If a patient has further extension of VTE or recurrent VTE despite already being established on a higher than standard dose of LMWH, discuss case with Haematology team as checking anti-Xa level to guide further dose escalation of LMWH may be appropriate.

4.2 Thrombocytopenia

- Cancer-associated VTE in the setting of thrombocytopenia provides additional challenges to balancing risks of bleeding and recurrent VTE.
- Despite the increased bleeding risk in patients with both cancer-associated VTE and thrombocytopenia, the risk of recurrent VTE is also increased four-fold.
- The initial 30 days following an acute VTE is the highest risk time for recurrence and therefore this needs to be considered when deciding treatment plan in these patients.
- There is a lack of data for the use of DOACs in patients with thrombocytopenia and the evidence suggests that DOACs have an increased risk of bleeding compared to LMWH.
- Patients with cancer-associated thrombosis and a platelet count of $\geq 50 \times 10^9\ L^{-1}$, can be treated with full dose anticoagulation without platelet transfusions.
- Patients with cancer-associated thrombosis and a platelet count of $< 50 \times 10^9\ L^{-1}$, need to be managed in accordance with the below flowchart.
- Patients with a **high risk of thrombus progression** include:
    - symptomatic central or segmental PE
    - proximal DVT
    - history of recurrent or progressive VTE
- Patients with have a **low risk of thrombus progression** include:
    - incidental subsegmental PE
    - distal DVT
    - catheter-related thrombosis

The below flow charts apply to patients with cancer-associated thrombosis and platelet count of <50x10^{9} L^{-1}.





4.3 Catheter-related thrombosis (CRT)

- Patients with cancer often require insertion of a central venous access device (CVAD) for administration of chemotherapy. However, thrombosis can complicate their use. Symptomatic CRT occurs in around 3% of patients.
- CRT may lead to PE in up to 10-15% of patients and loss of venous access in around 10% of patients.
- Catheters inserted on the right side, in the jugular vein, and with the distal extremity of the central catheter located at the junction of the superior vena cava and the right atrium (not in the right atrium), carry the lowest risk of CRT. PICC-lines carry a higher risk of CRT than Hickman lines or ports.
- Treatment for CRT should be made on an individual patient basis taking into account if the CVAD is functioning and the ongoing need for CVAD for future treatment.
- Options for anticoagulation include LMWH and DOACs.
- Anticoagulant treatment is recommended for a minimum of 3 months, but longer if the central venous catheter remains in place.
- If the CVAD is well-positioned, not infected and functioning, then there is no need to remove the line.
- In patients with symptomatic CRT, if symptoms persistent after 4 weeks of anticoagulation, then the CVAD should be removed. Anticoagulation should be continued for a minimum of 3 months, even if the CVAD has been removed.
- If there is evidence of superior vena cava syndrome related to CRT, then thrombolysis should be considered if appropriate.

4.4 Bleeding patients

- Patients who are actively bleeding require a careful risk assessment between the balances of bleeding vs thrombosis. This will need to be regularly re-assessed and treatment changed appropriately based on this.
- Factors which may contribute to a high thrombosis risk include the following, although this list is not exhaustive;
    - Acute VTE, within last 30 days
    - High risk of thrombus progression (see section 4.2)
- Factors which may contribute to a high bleeding risk include the following, although this list is not exhaustive;
    - GI or urothelial malignancy, particularly if on DOAC
    - Thrombocytopenia (see section 4.2)
    - Poor renal function
- Management options for these patients will need to be made on an individual patient basis depending on the balance of bleeding vs thrombosis. Additional advice on individual cases can be sought from Haematology.

4.5 IVC filters

- Insertion of an inferior vena cava (IVC) filter is reserved for use only in those patients with acute VTE (<30 days) and a contraindication to anticoagulation. The contraindication to anticoagulation should be short-lived, not long-term. For example, acute bleeding episode. Please seek advice from the Haematology team in these cases.
- IVC filters are **not** recommended for those suffering from recurrent VTE or in chronic VTE.

4.6 Brain tumors

- Intracranial haemorrhage (ICH) is a common and potentially life-threatening complication of both primary and secondary brain tumors, and complicates decisions regarding anticoagulation.
- Some tumors have a higher rate of spontaneous ICH than others, which should be considered when balancing the risk vs benefit of anticoagulation. These include melanoma, renal cell carcinoma, thyroid cancer, hepatocellular cancinoma and choricarcinoma.
- Evidence is limited regarding choice of anticoagulant in this context.
- **Primary brain tumors**; appear to have a 3 fold increase in ICH in patients treated with LMWH, however DOACs doesn't appear to increase the risk of ICH.
- **Brain metastases**; No increase in the risk of ICH has been seen in patients treated with either LMWH or DOACs.

4.7 End of Life patients

- Primary thromboprophylaxis is not appropriate for patients who are receiving end of life care (EoLC).
- If a patient who is being treated for a CAT is commenced on EoLC, their anticoagulation should be reviewed at this point. This is to ensure that anticoagulation isn't continued inappropriately in the final few days or weeks of a patient's life.

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