Clinical Guideline

CANCER PATIENTS REQUIRING THERAPEUTIC ANTICOAGULATION

SETTING Trust-wide

FOR STAFF Medical staff caring for patients with cancer who require anticoagulation

PATIENTS Adult patients with cancer requiring anticoagulation

CONTENTS:

Please note that this guideline does not cover standard VTE risk assessment or thromboprophylaxis regimes. All patients who are admitted to hospital should have a VTE risk assessment done. Patients admitted for routine chemotherapy are regarded as medical patients without reduced mobility.

SECTION 1: INTRODUCTION:

Correct management of anticoagulation in patients diagnosed with cancer is an important safety issue. This document is designed as a **guide** to available options. Decisions will be based on discussion between the clinician and the patient, taking into consideration risk factors for thrombosis and bleeding, cancer treatment regime and patient preference.

Patients may already be anticoagulated for a variety of reasons and factors that need to be taken into consideration include:

- Risks of withholding anticoagulation
- Risks of continuing anticoagulation (usually in relation to risk of bleeding)
- Interactions between systemic anticancer therapy (SACT) regimes or supportive medications and anticoagulant drugs

It is important to remember that malignancy itself increases venous and arterial thrombotic risk, but may also increase bleeding risk.

The majority of patients on pre-existing anticoagulation will be on oral drugs:

- Warfarin
- DOACs (Direct Oral AntiCoagulants also known as NOACs)

Warfarin

Warfarin can be extremely difficult to manage in patients who are unwell, and/or undergoing SACT treatments. Other complications include numerous drug interactions, bleeding risk and the requirement for short acting drugs particularly during periods of thrombocytopenia.

DOACS general information

- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban

Bleeding risk is thought to be less than with warfarin, but mucosal bleeding may be a problem e.g. haematuria, menorrhagia/PV bleeding

Drug Interactions

There are fewer drug interactions compared to warfarin but interactions can still occur. See table below for examples of commonly used interacting drugs. The use of DOACs in combination with these drugs is not necessarily contra-indicated but care should be taken.

This is not an exhaustive list. More information about drug interactions can be found at https://www.clinicalkey.com/#!/browse/drugs. Please discuss with pharmacy or haematology SpR ([redacted]) if unsure.

TABLE 1: POTENTIAL SIGNIFICANT INTERACTIONS WITH DOACs IN CANCER PATIENTS				
Inhibitors (enhance anticoagulant effects, increase risk of bleeding)				
Azole antifungals Ketoconazole Itraconazole Voriconazole Posaconazole Fluconazole	**Protease inhibitors** Ritonavir	**Immunosuppressive drugs** Cyclosporine Tacrolimus	**Anticancer drugs** Imatinib Crizotinib Vemurafenib Bicalutamide Encorafenib	**Other** Clarithromycin Erythromycin Abiraterone
Inducers (reduce anticoagulant effects, increase risk of thrombosis)				
Anti-epileptics Carbamazepine Phenytoin	**Other** Rifampicin St John's Wort	**Anticancer drugs** Enzalutamide Bexarotene Paclitaxel (not docetaxel) Encorafenib Dabrafenib		

Drug levels:

In general DOAC levels are not needed. However there are certain clinical situations which warrant DOAC level measurement (e.g. low/high BMI, poor renal function, concurrent use of interacting drugs, treatment failure). Discuss with haematology registrar ([redacted]) if level required.

All DOACs can be measured – use the drug name in the search function on ICE
Trough levels are taken immediately before the dose is due
Peak levels are taken 2-3hrs after the dose is taken.
Random levels may be of use in the event of bleeding, treatment failure, or if invasive procedures planned.

SECTION 1.1: Options for anticoagulation

Choice of DOAC

Apixaban: Can be started immediately in acute VTE. It is given twice daily which is felt to have PK advantages with fewer high peaks and low troughs, and less impact of missing a single dose. There is some evidence to support a lower bleeding risk.

Rivaroxaban: Once daily may be preferable for some patients (an initial 3 weeks of BD therapy is required). Can be started immediately in acute VTE. Needs to be taken with food. Concerns over GI bleed risk in patients with GI cancers

Edoxaban: Once daily which may be preferable for some patients but requires 5 days LMWH ***before*** starting the drug if used in acute VTE. Has the best drug interaction profile.

Dabigatran: If used in acute VTE requires 5 days LMWH ***before*** starting drug, concerns over accumulation in renal impairment. Does have an available reversal agent

Low molecular weight heparins (LMWH)

Patients admitted from other Trusts may be on alternative low molecular weight heparins
E.g. dalteparin (Fragmin®) or tinzaparin (Innohep®)
If the patient will have their ongoing care provided solely by UHBristol it is reasonable to switch their drug to enoxaparin (Clexane®). If switching to enoxaparin, give first dose when next dose of alternative LMWH would be due.

If this is not possible then refer to the individual drug's Summary of Product Characteristics (SPC) for specific advice regarding dosing – this can be found at https://www.medicines.org.uk/emc. General principles regarding safety of surgical/invasive procedures remain the same.

AntiXa monitoring

AntiXa levels are taken 3-4hrs after the dose. Therapeutic ranges at UHBristol laboratory:

- **Once** daily 1.5mg/kg dosing is 0.8-1.6iu/ml
- **Twice** daily dosing 1mg/kg twice daily range is 0.5-1.1iu/ml

If antiXa monitoring is indicated, e.g. in renal dysfunction, suggest check an antiXa level after the 3rd or 4th dose and thereafter weekly – frequency may be reduced if renal function and level remains stable but no less frequent than monthly.

Anticoagulation with thrombocytopaenia

Requires careful assessment of thrombotic risk vs bleeding risk

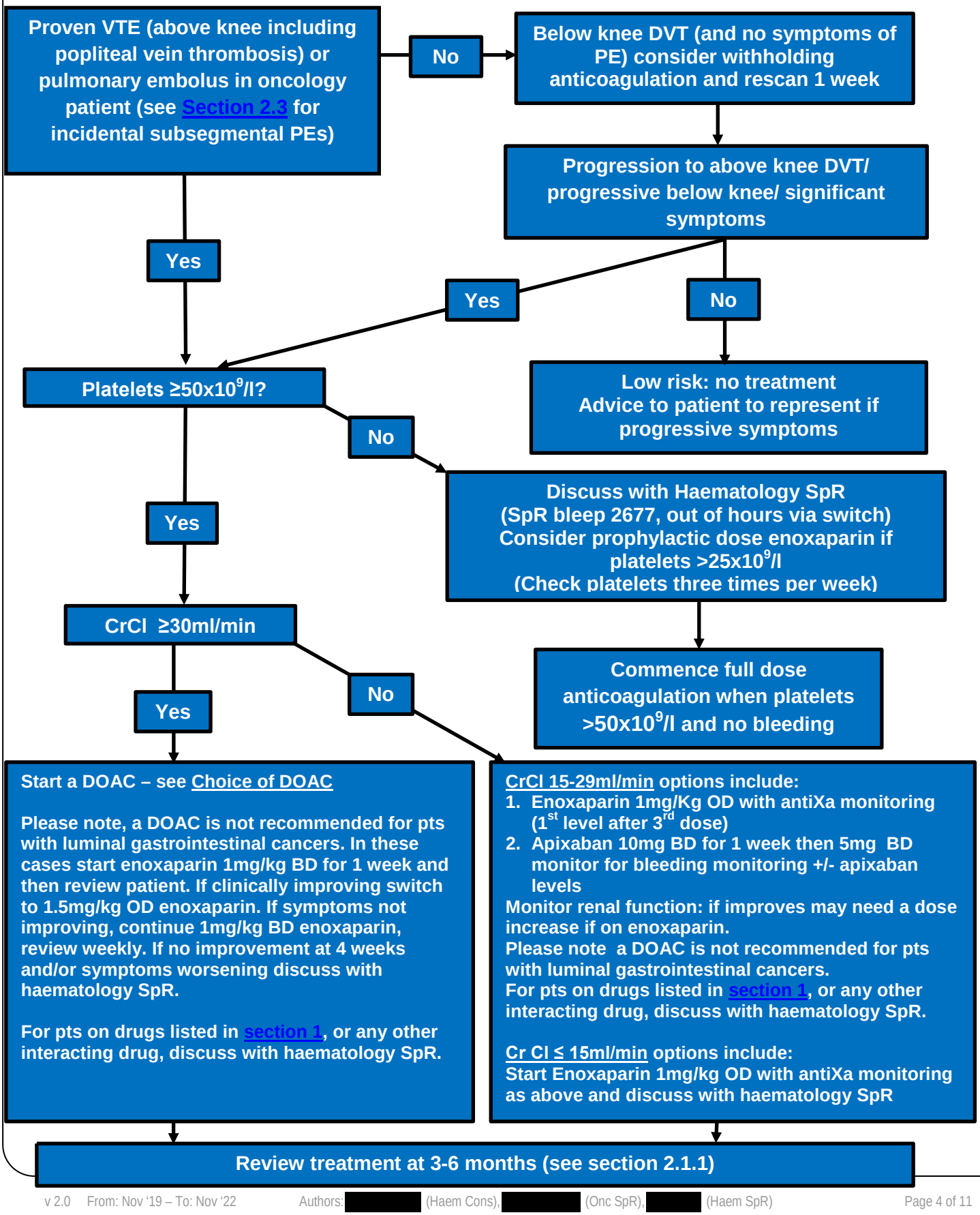
Platelets > 50x10^9/l	Full anticoagulation (monitor for bleeding)
Platelets 25-50x10^9/l	If high thrombotic risk (e.g. thrombotic event within last 3 months) use prophylactic anticoagulation (monitor for bleeding). All other patients stop anticoagulation when plts<50 x10^9/l.
Platelets <25x10^9/l	Avoid anticoagulation in all patients

Consider platelet transfusion to maintain platelets > 50x10^9/l if thrombosis within last 4-6 weeks (discuss with haematology SpR)

SECTION 2: MANAGING PATIENTS WITH NEW DIAGNOSIS OF VTE

SECTION 2.1 Patients presenting with venous thromboembolism in association with current cancer diagnosis

Previous evidence has suggested LMWH over warfarin[1] in patients with malignancy associated VTE. However, current evidence suggests DOACs are non-inferior to LMWH in these patients[2]. See above for information on individual DOACs.
For primary brain tumours please see Section 2.1.3



SECTION 2.1.1 Duration of treatment

For patients on enoxaparin, treatment should be reviewed at 3 months. If the patient is asymptomatic and their cancer is in remission then treatment can be stopped at this point (including for those pts with PE). Otherwise consider switching to a DOAC, or continuing enoxaparin. Therapy should be reviewed again at 6 months. For patients for whom this was their first VTE, and whose cancer is in remission, then anticoagulation can be discontinued at this point.

For patients whose cancer remains active, the CLOT trial[1] recommends considering lifelong anticoagulation. This should be a personalised decision for each patient taking into account thrombotic risk, risk of bleeding and patient preference. If the decision is made to continue treatment then for some patients reduced intensity anticoagulation may be appropriate e.g. apixaban 2.5mg BD or rivaroxaban 10mg OD. In uncomplicated patients there is no evidence for continuing enoxaparin beyond 6 months, so these patients should be considered for switch to an oral agent.

Where the decision is unclear consider referral for review in the bleeding and thrombosis clinic ([redacted]).

SECTION 2.1.2 PICC associated venous thromboembolism

Consider if the line needs to remain in situ. It is recommended that the line is removed if infected, poorly functioning or if symptoms persist after anticoagulation.

- If the line remains in situ the patient should be anticoagulated for at least 3 months and/or until line removal. Choice of anticoagulant is as per the flowchart in section 2.1.
- If the line is removed the patient should be anticoagulated for at least 6 weeks. Consider waiting for 24hrs post commencement of anticoagulation before removing the PICC to reduce the risk of embolisation. If this is not possible then at a minimum avoid removing line out of hours, unless the patient is septic.

SECTION 2.1.3 Anticoagulation of primary and secondary brain tumours

Thrombosis in patients with primary brain tumours presents difficulties as primary brain tumours are highly thrombogenic but also have a very high risk of bleeding (bleeding risk of up to 20% with anticoagulation). As always, carry out a risk benefit analysis. Options include:

- Enoxaparin (1mg/kg BD) for 2 weeks and then reducing the dose (1.5mg/kg OD).
- Use of a DOAC. There is some evidence that DOACs are not associated with additional bleeding risk over and above LMWH, and indeed may even have a lower bleeding risk[3].
- If bleeding risk is very high consider admission to the ward for iv heparin for 5 days (after discussion with haematology SpR).

Patients with secondary brain tumours should be treated as per the flowchart in Section 2.1.

SECTION 2.2 Patients with progressive/recurrent venous thromboembolism despite anticoagulation:

NB. In a patient with progressive/recurrent thrombosis always consider the possibility of progression/relapse of their underlying malignancy.

1. Check compliance with current therapy.
2. **If possible** check drug level (LMWH – antiXa level 3hrs after dose: DOAC level 2-3 hrs

after dose request on ICE using drug name in 'search')
3. Recommendation to switch to enoxaparin 1mg/kg BD for 2-4 weeks and discuss with haematology SpR.

Discuss with haematology SpR if already on this regime or if other concerns.

SECTION 2.3 Management of incidental venous thromboembolism:

Pulmonary emboli or (less commonly) deep vein thrombosis may be picked up incidentally on a staging/monitoring CT scan. In general the recommendation is to treat these as per the guidance in section 2.1.

The exception to this is incidental, asymptomatic, sub-segmental PEs. Currently these have not been found to have a survival disadvantage. Therefore anticoagulation can be withheld if concerns over high bleeding risk and no evidence of DVT (NB. 80% of patients with a coexisting DVT will not have leg symptoms)

If a patient is diagnosed with an 'incidental' PE:

1. Reassess patient to exclude symptoms of PE.
2. If symptoms present and/or patient is low risk for bleeding manage as per section 2.1
3. If definitely asymptomatic and high risk for bleeding request bilateral lower limb Doppler ultrasound.
   - If no DVT then it is reasonable to withhold anticoagulation. Give information to patient about symptoms and signs of DVT/PE to re-present if develops symptoms.
   - If DVT present then risk balance favours anticoagulation as per section 2.1

SECTION 3: MANAGING PATIENTS ON PRE-EXISTING ANTICOAGULATION WHO ARE DUE TO START ANTI-CANCER TREATMENT

SECTION 3.1 Atrial fibrillation (AF):

It may be preferable to stop anti-coagulation, particularly if the patient has a high chance of bleeding with anti-cancer treatment. Assess as below:

1. Document patients $CHADS_2VASC_2$ score as this is important in assessing underlying risk of stroke and will influence decision making if anticoagulation needs to be temporarily discontinued.
   https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk
2. Document bleeding risk associated with disease or treatment e.g. likelihood/duration of thrombocytopenia site/nature of tumour
3. Document current renal function and assess likelihood of renal impairment with treatment regime (particularly important with non-warfarin anticoagulants). Ensure dose appropriate for renal function: http://www.medicines.org.uk/emc/
4. Check that there are no important drug interactions: http://www.medicines.org.uk/emc
5. Assess patient preference and discuss the risks and benefits with the patient.
6. A decision to suspend, stop or switch anticoagulation should be clearly documented in the notes and communicated to the GP

3.1.1 Patients on warfarin:

Assess current warfarin control: historical INRs on ICE (check ICE OpenNet for Weston, North Bristol and RUH results) or check hand held records for GP near patient testing monitoring.

Options:

1. **Continue warfarin with close monitoring of INR**
   This is suitable for situation where it is felt that overall bleeding risk is low and there is a low likelihood of warfarin control being adversely influenced by treatment regime.
   It is very important that the need for SACT/radiotherapy is communicated to the team overseeing the patient's warfarin control.
2. **Switch to an alternative oral agent (Apixaban or Rivaroxaban)**
   This is suitable for patients where there is a high likelihood of erratic warfarin control with the proposed treatment regime. It may also be suitable for patients where there is likely to be a mild predictable thrombocytopenia as the half-life of these drugs is shorter than warfarin
3. **Switch to Enoxaparin**
   CrCl >30ml/min: Treatment dose 1.5mg/kg daily
   CrCl 15-30ml/min: Treatment dose 1mg/kg daily with antiXa monitoring after 3rd or 4th dose and then weekly initially reducing frequency if renal function and antiXa levels are stable.
4. **Stop anticoagulation**
   Especially if low $CHADS_2VASC_2$ score and high risk of bleeding.

3.1.2 Patients on DOACs (Apixaban, Dabigatran, Edoxaban, Rivaroxaban):

Many patients will be able to continue with these agents with careful monitoring of renal function and risk factors for bleeding.

Options:

1. **Continue with current treatment regime**
   - Assess renal function and adjust dose as per SPC (http://www.medicines.org.uk/emc/)
   - Check for interactions (see table in Section 1)
   - Assess liver function and adjust dose as per drug SPC

2. **Reduce dose**
   All DOACs have two dosing regimens for AF and the lower dose may be appropriate if concerns over bleeding associated with diagnosis
   - Apixaban 2.5mg bd
   - Dabigatran 110mg bd
   - Edoxaban 30mg OD
   - Rivaroxaban 15mg OD
3. **Switch to Enoxaparin**
   CrCl >30ml/min: Treatment dose 1.5mg/kg daily

   CrCl 15-30ml/min: Treatment dose 1mg/kg daily with antiXa monitoring after 3rd or 4th dose and then weekly initially reducing frequency if renal function and antiXa levels are stable.
4. **Stop anticoagulation**
   Especially if low $CHADS_2VASC_2$ score and high risk of bleeding.

3.1.3 Patients on LMWH:

It is most likely that the patient has been switched to low molecular weight heparin because of their cancer diagnosis and/or to allow for surgery/diagnostic procedures to be undertaken.

It is appropriate to discuss with them the options above so that they do not need to continue injections long term

SECTION 3.2 Patients with mechanical heart valves:

Apixaban, Edoxaban, Dabigatran, Rivaroxaban are contraindicated in patients with mechanical heart valves. Patients with tissue valves can be on these drugs.

1. Assess thrombotic risk of valve:
   - Site/type (mitral and tricuspid positions and older varieties e.g. ball and cage are associated with higher thrombotic risk)
2. Consider INR target range:
   - If higher than 2.5 then the patient is likely to be at higher thrombotic risk.

Options:

1. **Continue Warfarin with careful and more frequent INR monitoring**
   Ensure that the relevant anticoagulation dosing service is aware that the patient has started SACT.
2. **Switch to Enoxaparin 1mg/kg twice daily with antiXa monitoring (discuss with haematology SpR)**
   - Advantages:
     - Shorter duration of action
     - Evidence for lower bleeding risk compared to warfarin.

   - Disadvantages:
     - The evidence base for effectiveness of LMWH in mechanical valves is not strong, especially over prolonged time periods.

SECTION 3.3 Patients with previous venous thromboembolism (not associated with current cancer diagnosis)

Assess thrombotic history

- Site of previous thrombosis

- When thrombotic episode occurred (if within 3-6 months consider it to be associated with this cancer diagnosis)
- Underlying risk factors for thrombosis e.g. high thrombotic risk patients include patients with recurrent unprovoked VTE (especially if event occurred whilst adequately anticoagulated, underlying antiphospholipid syndrome, type of malignancy etc.)

Assess bleeding risk associated with planned treatment regime, especially

- Likelihood of thrombocytopenia including predicted severity and duration
- Risk of bleeding with tumour site e.g. high risk sites such as luminal UGI
- **In the absence of an acute thrombotic episode (3 months) therapeutic anticoagulation should be withheld if platelets <50x10^9/l**

Assess renal and liver function at baseline

- Consider likelihood of deterioration associated with treatment

3.3.1 Patients on warfarin:

Unless planned treatment is very unlikely to interfere with warfarin control or increase risk of bleeding it is often best to switch to alternative agents to manage these patients during treatment. If INR control is historically poor then that supports the decision

Options:

1. **Switch to Enoxaparin**
   - **Therapeutic dose** if history of aggressive recurrent VTE esp. if VTE on treatment
     - CrCl >30ml/min: Treatment dose 1.5mg/kg daily
     - CrCl 15-30ml/min: Treatment dose 1mg/kg daily with antiXa monitoring after 3rd or 4th dose and then weekly initially reducing frequency if renal function and antiXa levels are stable.
   - **Prophylactic dose** (standard dose 40mg OD; if <50Kg: 20mg; if >100Kg: 40mg BD) may be sufficient especially if concerns over bleeding risk.
2. **Switch to a DOAC**
   See 'Choice of DOAC', some patient may be eligible for reduced intensity anticoagulation

3.3.2 Patients on DOACS:

1. **Continue with current treatment regime**
2. **Use a reduced intensity regime**
   The following are licensed for long term prevention of recurrent VTE (consider discussion with haematology SpR): **Apixaban** 2.5mg BD; **Rivaroxaban** 10mg OD
3. **Switch to Enoxaparin**
   Therapeutic or prophylactic dose see above

3.3.3 Patients on LMWH:

These patients should remain on LMWH unless specific reason not to or patient unable to comply.

SECTION 4: MANAGING PATIENTS ON ANTICOAGULATION UNDERGOING SURGERY/INVASIVE PROCEDURES:

See Trust guidance for individual drugs (see below for links).

If unsure about the bleeding risk associated with a procedure/operation always discuss with the person doing the procedure to help with risk assessment.

NB. Surgery within 4 weeks of a new diagnosis of VTE is associated with high risk of progressive VTE. If possible surgery should be delayed but the risks of delaying surgery may outweigh the risks of proceeding. A careful plan for peri-operative anticoagulation will need to be made.

Lumbar puncture/intrathecal chemotherapy:

Treat as high bleeding risk/major surgery

Bone marrow biopsies:

Depending on the indication for anticoagulation and other risk factors for bleeding it may be appropriate to continue anticoagulation peri-procedure.

Patients on warfarin with an INR <3.0 with no other risk factors for bleeding can safely have a bone marrow aspirate and trephine.
NB. Check platelet count and INR within 24hrs of procedure.

For patients on LMWH and DOACS it is reasonable to hold off the morning dose, if applicable. Remember that DOACs reach peak concentration at around 3 hours and LMWH at 4 hours.

References

1. Agnes Y.Y. Lee *et al*. Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer, N Engl J Med 2003; 349:146-153.
2. Raskob G *et al*. Edoxaban for the treatment of cancer-associated venous thromboembolism. NEJM 2018; 378(7): 615-624.
3. Carney *et al*. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. J Thromb Haemost. 2019;17(1):72-76.

RELATED DOCUMENTS

Links to Trust documents relating to DOACS

NOACS/DOACS a quick guide
(Information on dosing and cessation of drugs for planned procedures)
http://nww.avon.nhs.uk/dms/Download.aspx?did=18640
NOAC: Apixaban Eliquis Or Rivaroxaban Xarelto: Management Of Haemorrhage And Or Emergency Surgery
http://nww.avon.nhs.uk/dms/Download.aspx?did=18642
NOAC: Dabigatran Pradaxa Management Of Haemorrhage And Or Emergency Surgery
http://nww.avon.nhs.uk/dms/Download.aspx?did=18641

Links to Trust Documents relating to warfarin

Managing patients on warfarin requiring emergency surgery
http://nww.avon.nhs.uk/dms/Download.aspx?did=16231
Emergency warfarin reversal (critical bleeding)
http://nww.avon.nhs.uk/dms/Download.aspx?did=15315

Elective surgery in patients on warfarin

http://nww.avon.nhs.uk/dms/Download.aspx?did=13150

Links to Trust documents relating to Low Molecular Weight Heparin
Clinical guideline for use of low molecular weight heparin within UHBristol
http://nww.avon.nhs.uk/dms/Download.aspx?did=13639

AUTHORISING BODY	BHOC Systemic Anticancer (SACT) Group, Bristol Haematology and Oncology Centre
SAFETY	Patients should never be prescribed LMWH and a DOAC concomitantly.
QUERIES	The consultant supervising the patient's care should be consulted For specific anticoagulation related queries Contact haematology SpR on [redacted] or out of hours via switch.