Broad Recommendations / Summary

This guidance should be used for all patients presenting with Cancer Associated Venous thromboembolism (CAT).

**Venous thromboembolism** is the collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). It is more frequent and is complex to manage in patient with malignant disease. Cancer patient’s risk of VTE is seven-fold greater than general population, with a tendency to develop both arterial and venous thromboembolism particularly while receiving systemic chemotherapy. This often causes significant morbidity and mortality. Patient with cancer associated VTE also have a high risk of recurrence on treatment than those without cancer.

**Active cancer** can be defined as cancer: receiving active antimitotic treatment; or diagnosed within the past 6 months; or recurrent or metastatic; or inoperable. This excludes squamous skin cancer and basal cell carcinoma.

For active cancer, anticoagulation therapy can include treatment with LMWH or DOACs (Direct-acting oral anticoagulant) (NICE guideline; updated March 2020)

Meta-analysis of 2 RCTs (Randomised Control trial- Hokusai VTE and Select-D) has shown DOACs to have lower 6-months recurrent VTE when compared with LMWH (RR 0.65; 95% CI 0.42-1.01). DOACs had higher major bleeding when compared to LMWH (RR 1.74 95% CI 1.05-2.88). Similarly, CRNMB (clinically relevant non-major bleeding) was higher (RR 2.31 95% CI 0.85-6.28)(1). Despite of no difference in mortality (RR 1.03, 95% CI0.85-1.26) and lower rate of recurrent VTE benefit of these oral agents was limited by the increased risk of bleeding associated with their use. However, recently published RCT (Caravaggio) has shown Apixaban to be noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism (Recurrent VTE occurred in 5.6% in the apixaban group and 7.9% in Dalteparin group; hazard ratio, 0.63; 95% confidence interval [CI], 0.37 to 1.07; P<0.001 for noninferiority) without an increased risk of major bleeding (3.8% in the apixaban group and in 4.0% in the dalteparin group, hazard ratio, 0.82; 95% CI, 0.40 to 1.69; P=0.60)(2).

Currently NICE has guideline for treatment of DVT and PE in active cancer patients (3)

1.3.15 Offer people with **active cancer** and confirmed proximal DVT or PE anticoagulation treatment for 3 to 6 months. Review at 3 to 6 months according to clinical need. For recommendations on treatment after 3 to 6 months see the section on **long-term anticoagulation for secondary prevention**. [2020]

1.3.16 When choosing anticoagulation treatment for people with active cancer and confirmed proximal DVT or PE, take into account the tumour site, interactions with other drugs including those used to treat cancer, and the person’s bleeding risk. [2020]

1.3.17 Consider a direct-acting oral anticoagulant (DOAC) for people with active cancer and confirmed proximal DVT or PE. [2020]

1.3.18 If a DOAC is unsuitable consider LMWH alone or LMWH concurrently with a VKA for at least
5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own. [2020]

1.3.19 For people with confirmed DVT or PE and cancer that is in remission, follow the recommendations in the section on anticoagulation treatment for confirmed DVT or PE. [2020]

Here we provide guidance for prescribing rivaroxaban or apixaban for CAT, risk assessment, consideration for special population and monitoring of cancer patients on rivaroxaban/apixaban (4).
094 - Procedure for Use of DOACs (Rivaroxaban/Apixaban) for treatment of Cancer Associated VTE

1 Purpose/legal requirements/background

To ensure best practice is adhered to with respect to management of patients with active cancer and suspected or proven VTE with Rivaroxaban or Apixaban.

2 Policy/Procedure/Guideline details

This guideline applies to all medical and nursing staff involved in the care of patients with active cancer and suspected or proven VTE.

Duties

Doctors: -
- To ensure patients with suspected or proven VTE are managed as per trust guideline.
- To ensure that adequate information is provided to the GP surgery on discharge.
- To comply with all required training in oral anticoagulation.
- To comply with required training for managing cancer associated thrombosis (CAT).

Nurses: -
- To ensure that Rivaroxaban or apixaban are delivered as described in the guideline.
- To ensure that adequate information is provided to the GP surgery on discharge.
- For patients presenting to Incidental pulmonary Embolism (IPE) pathway –
  - To ensure Blood tests including FBC, BCP, Clotting, D-Dimer
  - To ensure completion of documents Including IPE- Initial assessment form, IPE- Hull score, IPE- PESI score (ARIA questionnaires/paper forms)
  - To ensure subsequent follow up as per pathway
3 Content

Oral options for CAT management

DOACs are approved for the treatment of CAT in patients with a low risk of bleeding and where there are no anticipated drug-drug interactions with their anticancer therapy or other contraindication.

A. Prescribing information for Rivaroxaban (5-7)

Initial Treatment of DVT/PE

15 mg twice daily for first 3 weeks (to be taken with food)

Secondary Prophylaxis

20 mg once daily (to be taken with food) for the continued treatment.

Empirical dose reduction for Patients ≥75 years

- Initial treatment dose of 10 mg twice daily for 3 weeks
- Followed by secondary thrombo-prophylaxis at 15 mg once daily

B. Prescribing information for Apixaban (7-9)

- Initial 10 mg twice daily for 7 days
- Maintenance 5 mg twice daily.

- No dose adjustment required for elderly.

C. Length of Anticoagulation

- For 3-6 months
- Beyond 6 months- treatment will need to be individualized (NICE, ASCO and ACCP guidelines)

D. Special situations

Missed dose:

Rivaroxaban:

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21)

- The patient should take Rivaroxaban immediately to ensure intake of 30 mg per day. In this case two 15 mg tablets may be taken at once.
- The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
If a dose is missed during the once daily treatment phase

- The patient should take Rivaroxaban immediately and continue on the following day with the once daily intake as recommended.
- The dose should not be doubled within the same day to make up for a missed dose.

**Apixaban:**

If a dose is missed, the patient should take Apixaban immediately and then continue with twice daily intake as before.

For patients who are unable to swallow whole tablets

- Tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.
- The crushed tablet may also be given through gastric tubes in a small amount of water.

**E. Contraindication:**

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications (Prefer Dalteparin over DOACs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Creatinine Clearance &lt; 30ml/min (Using Cockcroft-Gault equation)</td>
</tr>
<tr>
<td>Active clinically significant bleeding</td>
<td>Child Pugh A and Liver function tests &gt; 3x Upper limit of normal,</td>
</tr>
<tr>
<td>Lesions or condition considered to be a significant risk of major bleeding.</td>
<td>Expected malabsorption at stomach or small bowel (feeding tube, gastric or bowel resection)</td>
</tr>
<tr>
<td>Concomitant treatment with any other anticoagulants</td>
<td>Active genitourinary (GU) or gastrointestinal (GI) – ‘luminal’-lesions</td>
</tr>
<tr>
<td>Hepatic disease associated with Coagulopathy and Child Pugh B and C</td>
<td>A body weight &lt;50 or &gt;150 kg</td>
</tr>
<tr>
<td>Pregnancy and breast feeding</td>
<td>Use of any antiplatelet agent other than Aspirin 75 mg daily</td>
</tr>
<tr>
<td></td>
<td>Any suspected significant drug interaction (that can cause increase/reduce anticoagulant effect).</td>
</tr>
</tbody>
</table>
DOACs are not associated with an increased incidence of intracranial haemorrhage relative to LMWH in patients with brain metastases or primary brain tumours and can be prescribed safely(10).

**Patient Choice**
For patients that ordinarily Dalteparin would be safer but for particular reasons (e.g. needle phobia, patient choice-insistence etc. including a known contraindication to heparins) one can still consider DOACs after the patient is fully informed of the excess clinically relevant non major bleeding risk, they are accepting.

**F. Special Populations**

**Renal Impairment**

*Rivaroxaban*
- No dose adjustment from the recommended dose is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min)
- Patients with moderate (creatinine clearance 30 - 49 ml/min) renal impairment: Should be treated with 15 mg twice daily for the first 3 weeks. Thereafter 15 mg once daily should be considered.
- In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, rivaroxaban is not recommended

*Apixaban*
- no dose adjustment is necessary in patients with mild or moderate renal impairment
- In patients with severe renal impairment (creatinine clearance 15-29 mL/min) apixaban is to be used with caution
- In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, apixaban is not recommended

**Thrombocytopenia**

In presence of thrombocytopenia a risk-benefit balance of anticoagulation should be reassessed.
<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Anticoagulation with DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50 X 10^9/L</td>
<td>Full dose DOAC</td>
</tr>
<tr>
<td>&lt;50 X 10^9/L but ≥ 25 X 10^9/L</td>
<td>• Consider dose reduction for Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 10 mg PO BID during the first 3 weeks of treatment</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 15 mg PO daily after 3rd week</td>
</tr>
<tr>
<td></td>
<td>• No dose reduction is needed for Apixaban.</td>
</tr>
<tr>
<td></td>
<td>• If the platelet count is &lt;50 X 10^9/L from chemotherapy-induced thrombocytopenia, and</td>
</tr>
<tr>
<td></td>
<td>DOAC dose has been adjusted or held, a FBC with platelet count will need to be repeated</td>
</tr>
<tr>
<td></td>
<td>in 5-7 days</td>
</tr>
<tr>
<td></td>
<td>• If the thrombocytopenia (&lt;50 X 10^9/L) persists for at least 5-7 days, rivaroxaban or</td>
</tr>
<tr>
<td></td>
<td>Apixaban will be held</td>
</tr>
<tr>
<td></td>
<td>• If/when the platelet count recovers to &gt;50 X 10^9/L, the patient may be re-evaluated</td>
</tr>
<tr>
<td></td>
<td>for resumption of DOACs</td>
</tr>
<tr>
<td>&lt;25 X 10^9/L</td>
<td>Withheld for platelet count &lt;25 X 10^9/L, if the patient has acute PE that has caused</td>
</tr>
<tr>
<td></td>
<td>cardiorespiratory impairment and still in the initial acute treatment phase, consider</td>
</tr>
<tr>
<td></td>
<td>switching to LMWH with concurrent platelet transfusion if bleeding. Please take advice</td>
</tr>
<tr>
<td></td>
<td>from haematology</td>
</tr>
</tbody>
</table>

Haemodynamically unstable PE patients or patients who require thrombolysis

DOACs are not recommended

G. Screening for Drug Interaction

*Increased Anticoagulant Effect:*
- Azole Antimycotics
- HIV protease
- Dronaderone
**Reduced Anticoagulant Effect**

- Rifampicin
- Carbamazepine
- Phenytoin
- Phenobarbital
- St John’s wort

At initiation of DOACs, the **patient’s medication list** should be reviewed for interaction. Please check with pharmacist if in doubt who could peruse existing tools e.g. [https://about.medicinescomplete.com/publication/stockleys-drug-interactions/](https://about.medicinescomplete.com/publication/stockleys-drug-interactions/)

If a drug is found to preclude initiation of rivaroxaban during initial screening, efforts should be made to discontinue or substitute the problematic agent **if it is in the best interest of the patient to do so**, as determined by the treating Oncologist/Haematologist and in concert with the prescribing physician.

Patients should be instructed to contact the community anticoagulation service of any changes to drug regimen or medical situation, to **prompt re-evaluation** of possible drug interactions.

If a contra-indicated drug is later added, a similar attempt will be made to discontinue or substitute the agent.

**H. Monitoring of Patient Parameters**

Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs. (Please refer to trust guideline on Intranet- **379 - Management of Bleeding Patients on Antithrombotic Agents Guideline**)

- No routine anticoagulant monitoring required (INR tests are unreliable)
- Clotting parameters (e.g. PT, aPTT, INR) are affected
- If patient is deemed in need of monitoring anti-Xa activity can be requested (suggest discussion with haematologist)

4 **Process for monitoring compliance**
The thrombosis committee is responsible for monitoring compliance with this guideline. Use of DOACs for CAT will be audited following 6 months of guideline implementation in Queen’s Centre for Oncology and Haematology.
Authors may wish to use the tables below however these are not a requirement.

Appendix 1 - Duties (or included in the body of the document)
Please include details of the duties and requirements of staff groups if not made clear in the section 2 of the document.

<table>
<thead>
<tr>
<th>Title</th>
<th>Duties</th>
</tr>
</thead>
</table>

Appendix 2 – Definitions/Glossary (or included in the body of the document)
Please include details of the definitions used if not made clear in section 2 of the document.

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
</tr>
</thead>
</table>

References
