A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

<table>
<thead>
<tr>
<th>Version Number:</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does this version include changes to clinical advice:</td>
<td>Yes</td>
</tr>
<tr>
<td>Date Approved:</td>
<td>30th September 2020</td>
</tr>
<tr>
<td>Date of Next Review:</td>
<td>1st September 2023</td>
</tr>
<tr>
<td>Lead Author:</td>
<td>Catherine Bagot &amp; Cristina Coelho</td>
</tr>
<tr>
<td>Approval Group:</td>
<td>Medicines Utilisation Subcommittee of ADTC</td>
</tr>
</tbody>
</table>

Important Note:

The Intranet version of this document is the only version that is maintained. Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.
Apixaban, Edoxaban and Rivaroxaban (Factor Xa Inhibitors):

Management of haemorrhage, surgery or other invasive procedures

Introduction

Apixaban, edoxaban and rivaroxaban are direct oral anticoagulants (DOACs) that inhibit factor Xa activity. They have relatively short half-lives (8-12 hours) but longer in patients with significant renal impairment. In patients with normal renal function, for most elective procedures with a significant bleeding risk, omission of anticoagulant treatment for 48 hours pre-operatively should suffice.

Despite the availability of a new reversing agent (andexanet alfa), management of emergency surgery or bleeding situations will often remain challenging. At the present time there is limited evidence on which to base guidance for many situations. Much of the following advice is therefore largely empirical with a pragmatic view towards balancing the thrombotic and haemorrhagic risks facing anticoagulated patients requiring invasive procedures or experiencing major bleeding.
Elective minor invasive procedures (for which warfarin would not have been discontinued)

This would include standard dental procedures, routine upper and lower GI endoscopy +/-simple biopsy, joint injections and cataract extraction with lens implantation (posterior segment eye surgery or surgery involving the iris should be regarded as major surgery).

**Minor dental work:** Dental procedures with low or no bleeding risk can usually be undertaken without interrupting apixaban, edoxaban or rivaroxaban therapy, however for procedures with a higher bleeding risk a morning dose of these drugs should be omitted. Undertake dental procedure early in the day, limiting initial treatment area and assess bleeding before continuing. Actively consider suturing and/or packing. The deferred morning dose of the DOAC can be taken at least 4 hours after dental haemostasis has been achieved. Alternatively, if taking rivaroxaban or edoxaban once daily in the evening, this dose can be taken as normal (at least 4 hours after dental haemostasis has been achieved). See National guidance from the Scottish Dental Clinical Effectiveness Programme (SDCEP) for further advice [here](#).

**Joint injections:** Refer to rheumatology specialist advice if a patient anticoagulated with a factor Xa inhibitor is due to have a joint injection.

**Other minor procedures:** For endoscopy or cataract surgery it is recommended that the procedure is delayed until 24h after the last dose of apixaban, edoxaban or rivaroxaban. The next dose of anticoagulant should be deferred until 4-6h post procedure (or longer if haemostasis has not been achieved). If the patient has significant renal impairment (creatinine clearance [CrCl] <30 ml/min) the DOAC may have to be omitted for 48h pre-procedure.

---

**Low Bleeding Risk Procedure**

- **Omit Xa inhibitor for 24h prior to procedure**
  - [if CrCl <30 ml/min omit for 48h]
  - Creatinine Calculator available [here](#)
  - No pre-op LMWH required
  - Post-op
    - Defer restarting Xa inhibitor until adequate haemostasis is secured, and at least 4-6h post procedure
Elective procedures with moderate or high risk of bleeding

These will include most operations with any risk of bleeding (including endoscopies involving sphincterotomy or polypectomy), and procedures using neuro-axial anaesthesia.

Apixaban, edoxaban and rivaroxaban will need to be discontinued prior to the procedure, with the aim of achieving normal haemostasis. Pre-operative bridging therapy with low molecular weight heparin (LMWH) should not be required. All these factor Xa inhibitors are contra-indicated in patients with CrCl <15 ml/min.

Pre-op: Omit apixaban, edoxaban and rivaroxaban for 48h prior to major surgery, aiming for a normal prothrombin time (PT). However it should be noted that a normal PT does not exclude the possibility of therapeutic anticoagulant levels. If the patient has significant renal impairment [CrCl <30 ml/min] consider omitting the DOAC for 72h and checking drug level pre-operatively (desired level ≤ 25ng/ml measured by specific anti-Xa assay). It is recommended that calculated CrCl is used (rather than eGFR) when determining time for stopping apixaban, edoxaban or rivaroxaban pre-surgery – CrCl calculator available here.

Post-op: initial thromboprophylaxis will be most simply achieved with LMWH at prophylactic doses (starting at the later of 4h post-op or at 6pm on day of surgery, assuming adequate post-op haemostasis). Once post-op haemostasis is safely secured and bleeding risk has subsided DOAC can be re-introduced 48h post-op, assuming epidurals have been removed. At that stage, if there are particular concerns related to bleeding risk or if oral route is not available, LMWH may continue. LMWH dose should be determined based on thrombotic risk – prophylactic dose for patients deemed to have a low thrombotic risk, and therapeutic dose (e.g. enoxaparin 1mg/kg twice daily) for patients with a high thrombotic risk. The DOAC can be restarted 24h after the last dose of LMWH.

Neuro-axial anaesthesia

Neuro-axial and deep local anaesthetic blocks should be regarded as a major invasive procedure for the purposes of this guidance. Catheter-directed local anaesthetic techniques should not be used during apixaban, edoxaban or rivaroxaban treatment. There should be an interval of at least 6 hours after the removal of an epidural catheter before the introduction of apixaban, edoxaban or rivaroxaban and frequent observation for neurological signs/symptoms of epidural haematoma must be made.
**Moderate or High Bleeding Risk Procedure**

**Omit Xa inhibitor for 48h prior to procedure**
- [if CrCl <30 ml/min omit for 72h]
- Creatinine Calculator available [here](#)

**No pre-op LMWH required**

**Check Coagulation Screen Pre-op**
- Desired PT ≤ 13s and APTT < 38s
- [a normal PT and APTT does not exclude the possibility of therapeutic anticoagulant levels. If concern, consider checking pre-op drug level by anti-Xa assay]

**Post-op**
1. Institute standard post-op thromboprophylaxis with low dose LMWH and anti-embolic stockings as appropriate
2. Defer restarting Xa inhibitor until:
   - adequate haemostasis is secured
   - at least 48h post procedure
   - at least 6h after removal of any epidural/spinal anaesthetic
3. The first post-op dose of Xa inhibitor can be given 24 hours after the last dose of LMWH [LMWH and a DOAC should not be prescribed concurrently]
Haemorrhage & emergency invasive procedures

Andexanet alfa is a new factor Xa inhibitor reversal agent that works as a decoy target to which the factor Xa inhibitors bind preferentially and therefore counteracts the anticoagulant effect of these agents.

Andexanet alfa is now licensed to reverse anticoagulation in situations of life-threatening or uncontrolled bleeding in patients taking apixaban or rivaroxaban.

Due to lack of clinical trial data, andexanet alfa is not licensed for use in patients taking edoxaban. However, based on the similarity of edoxaban’s mechanism of action when compared to apixaban and rivaroxaban, the off label use of andexanet alfa in patients taking edoxaban who present with life-threatening or uncontrolled bleeding is accepted across NHS GGC.

The routine use of andexanet alfa prior to invasive procedures is not recommended. The half life of andexanet alfa is considerably shorter than the half life of factor Xa inhibitors so post operative haemorrhage is a significant risk. Use prior to life saving interventions which cannot be delayed, and would go ahead regardless of anticoagulation reversal, may be authorised by haematology consultant in exceptional circumstances.

Andexanet alfa should only be prescribed following discussion with a haematology consultant.

Key principles in managing haemorrhage or emergency invasive procedures are:

1. Assess coagulation screen and renal function.
2. Ascertain time of the most recent dose of anticoagulant, and administer no further doses. If very recent ingestion (≤ 2h), consider administration of oral activated charcoal to inhibit further drug absorption. These anticoagulants are not dialysable.
3. Consider possibility of delaying major surgery until anticoagulant effect has sufficiently dissipated.
4. The use of antiXa monitoring may be of benefit if surgery cannot be delayed until anticoagulant effect has sufficiently dissipated. In normal working hours antiXa result (once sample arrived in laboratory) should be available within 2 hours; out of hours, result should be available within four hours.

If major surgery has to proceed in the face of significant anticoagulant effect:

- Ensure haemostatic platelet count & fibrinogen level & satisfactory pre-op Hb
- Treat any additional causes of coagulopathy
- Consider general haemostatic measures (e.g. 1g iv tranexamic acid)
- If despite the above measures there is significant peri- or post-op bleeding discuss with haematologist and consider administration of prothrombin complex concentrate (e.g. Beriplex® 50 units/Kg) or activated clotting factors (e.g. Feiba® 50 units/Kg)
- Andexanet alfa does not have a licence for reversal of anticoagulation prior to urgent surgery and should not be routinely used for this indication except in exceptional circumstances and only after discussion with a consultant haematologist
In the presence of life threatening or major uncontrolled bleeding:

- Follow general major haemorrhage principles – see separate algorithm (Appendix 2)
- Treat any additional causes of coagulopathy
- Consider general haemostatic measures (e.g. 1g iv tranexamic acid)
- Discuss with haematology consultant the appropriateness of andexanet alfa. Note that this medicine is only licensed for the reversal of apixaban and rivaroxaban. Use for reversal of edoxaban in off label
- When considering the use of andexanet alfa, the consultant responsible for the patient’s care should take into account the individual clinical circumstances of the patient, including the likely prognosis following a catastrophic bleeding event

The following must be considered prior to using andexanet alfa:

The bolus dose reverses the effect of the factor Xa inhibitor within 2 minutes and this persists during the subsequent continuous infusion. However, the half-life of andexanet alfa is one hour and much shorter than that of rivaroxaban (5-9 hours) or apixaban (12 hours). Clinicians must therefore be very alert to the restarting of bleeding in the 24 hours following the completion of the infusion.

- Andexanet alfa is administered as an IV bolus over 15-30 minutes followed by an IV infusion over 2 hours. Dose is calculated using the tables in page 7 (no dose adjustments are recommended for elderly patients or patients with renal or hepatic impairment). Instructions for administration can be found in Appendix 1 and on Medusa Injectable Medicines Guide (available here) – the use of a syringe driver is recommended.
- There may be circumstances where the appropriateness of using andexanet alfa is not entirely clear e.g. the patient does not meet the definition of life threatening/uncontrolled bleeding but the clinician feels that the bleeding is sufficient to warrant haemostatic support in addition to tranexamic acid. Beriplex 50IU/kg can still be used in those circumstances if the responsible clinician and consultant haematologist consider this to be appropriate.
- It is also possible that bleeding may resume despite the use of andexanaet alfa. Such situations should be discussed with a consultant haematologist and a decision made as to whether there is a role for the additional use of Beriplex 50 IU/kg
Factor Xa inhibitors: Management of haemorrhage and surgery

Written by: Dr Catherine Bagot and Cristina Coelho
Approved by: NHSGGC ADTC Medicines Utilisation Sub-Committee
Review Date: September 2023

<table>
<thead>
<tr>
<th>Factor Xa Inhibitor</th>
<th>Last dose taken</th>
<th>Timing of last dose before andexanet alfa infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 8 hours/Unknown</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>5mg or less</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>More than 5mg</td>
<td>High dose</td>
</tr>
<tr>
<td></td>
<td>or dose unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>10mg or less</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>More than 10mg</td>
<td>High dose</td>
</tr>
<tr>
<td></td>
<td>or dose unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>30 mg or less</td>
<td>Low dose</td>
</tr>
<tr>
<td>(off label)*</td>
<td>More than 30 mg</td>
<td>High dose</td>
</tr>
<tr>
<td></td>
<td>or dose unknown</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Initial Intravenous Bolus</th>
<th>Continuous Intravenous Infusion</th>
<th>Total number of vials required</th>
</tr>
</thead>
<tbody>
<tr>
<td>400mg at a target rate of 30 mg/min</td>
<td>4 mg/min for 120 minutes (480mg)</td>
<td>5</td>
</tr>
<tr>
<td>800mg at a target rate of 30 mg/min</td>
<td>8 mg/min for 120 minutes (960mg)</td>
<td>9</td>
</tr>
</tbody>
</table>

- AntiXa levels should not be measured to assess the effectiveness of andexanet alfa as antiXa levels do not correlate with clinical efficacy. If patient re-bleeds, discuss with haematology consultant.
- Andexanet alfa is a fridge item and cannot be returned to pharmacy. When requesting a supply, please specify the exact number of vials needed to treat the patient to avoid waste.
- Emergency supplies of andexanet alfa are located within the fridge section of the emergency drug cupboard at GRI, QEUH, RAH and IRH. Contact Pharmacy if a supply is required during working hours or the hospital coordinator if out of hours. Location of emergency fridges is detailed below:
  - GRI: Centre Block, outside main pharmacy department
  - QEUH: ARU, pharmacy POD room
  - RAH: Ward 10, antibiotic alert fridge
  - IRH: Ward L South, emergency cupboard fridge

**Once haemostasis is secured and/or invasive procedure is completed:**
- Continue to monitor haemostasis. If patient re-bleeds, discuss with haematology consultant.
- Prescribe thromboprophylaxis with LMWH as soon as appropriate.*
- If a DOAC is to be re-introduced this should be deferred until 24h after the last dose of LMWH.
- Andexanet alfa is a black triangle drug – report any suspected adverse reactions via Yellow Card Scheme here.

* The risk of thrombosis (arterial and venous) was reported in 10.3% of bleeding patients who received andexanet alfa in phase III/IV trials. This may reflect the patients’ underlying risk of thrombosis rather than a direct effect of andexanet alfa.
Appendix 1: Preparation and administration of andexanet alfa
Prepared for NHS GGC by Practice Development in collaboration with Medicines Information Team

For further information on dose requirements, preparation and administration refer to:

- Pages 5-7 of this guideline
- Medusa IV monograph

Andexanet alfa is available in vials containing 200mg powder for solution for infusion.

<table>
<thead>
<tr>
<th></th>
<th>Initial loading dose</th>
<th>Continuous maintenance infusion</th>
<th>Total number of vials required (loading and maintenance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>400mg At a target of 30mg/min (infusion rate approximately 180mL/hr)</td>
<td>480mg 4mg/min for 120mins (infusion rate 24mL/hr)</td>
<td>5</td>
</tr>
<tr>
<td>High dose</td>
<td>800mg At a target of 30mg/min (infusion rate approximately 180mL/hr)</td>
<td>960mg 8mg/min for 120 mins (infusion rate 48mL/hr)</td>
<td>9</td>
</tr>
</tbody>
</table>

Andexanet alfa is given by loading bolus dose followed immediately by maintenance infusion. The maintenance infusion should be commenced as soon as the loading dose is complete. This may involve starting the preparation of the maintenance dose immediately following the preparation of the loading dose due to rates of infusion and short infusion times.

In NHS GGC it is recommended that andexanet alfa IV infusion is given using a syringe infusion pump with an in-line 0.2 or 0.22micron low-protein filter. This may involve the preparation of multiple syringes for both loading dose and maintenance infusion.

Additional information: The Medusa IV monograph provides instructions on the use of a volumetric pump. However, this involves adding the reconstituted andexanet alfa to an empty, sterile polyolefin or PVC infusion bag. These are not commonly available in clinical areas across NHS GGC.
**Loading dose**

Give at a rate of approximately 30mg per minute

- Low dose – 400mg given over 15mins (infusion rate approximately 180mL/hr)
- High dose – 800mg given over 30mins (infusion rate approximately 180mL/hr)

**Instructions for reconstitution/preparation of loading dose:**

1. Reconstitute the required number of vials of andexanet alfa for the **low dose** regimen or **high dose** regimen. Inject 20mL sterile water for injections into each 200mg vial. Use 20 gauge (or larger) safety hypodermic needles. Slowly direct the stream down the wall of the vial. Gently swirl the vial (do not shake) until the powder is completely dissolved (this takes approximately 3-5 minutes for each vial). Inspect the reconstituted solution for particulate matter and/or discolouration prior to administration. Do not use if opaque particles or discolouration are present. Prepare all vials before the next step.

2. Withdraw the required volume of the reconstituted dose into 60mL syringes. For the **high loading dose**, you will need 2 x 60mL syringes.

3. Add the **in-line filter** and administration set and set the rate on the syringe pump to deliver 30mg per minute (infusion rate approximately 180mL/hr).

**Maintenance dose**

- Low dose – 480mg given as 4mg/min for 120 mins (infusion rate 24mL/hr)
- High dose – 960mg given as 8mg/min for 120mins (infusion rate 48mL/hr)

The maintenance infusion should be commenced as soon as the loading dose is complete.

**Instructions for reconstitution/preparation of maintenance dose:**

1. Prepare vials as before.

2. Withdraw the required volume of the reconstituted dose into 60mL syringes. For the **high maintenance dose**, you will need 2 x 60mL syringes.

3. Add the **in-line filter** and administration set and set the rate on the syringe pump to deliver **low dose** 4mg/min for 120 mins (infusion rate 24mL/hr), or **high dose** 8mg/min for 120 mins (infusion rate 48mL/hr).
Appendix 2: Management of haemorrhage in factor Xa inhibitor-treated patients

PATIENT RECEIVING APIXABAN, EDOXABAN or RIVAROXABAN THERAPY: HAEMORRHAGE PROTOCOL

STOP: anticoagulant

1. Check Coag screen (+/- drug level by anti-Xa assay)
2. Document time of last dose of DOAC [if < 2h consider oral activated charcoal]
3. Check FBC and renal function

MILD BLEED
- Mechanical compression
- Tranexamic Acid
  - i.v. 10 mg/kg
- Delay next rivaroxaban dose or discontinue treatment

MAJOR BLEED
- Maintain BP and Urine Output
- Optimise tissue oxygenation
- Control haemorrhage
  - Mechanical compression
  - Surgical / radiological intervention
- Tranexamic Acid (1g i.v.)
- Red cell transfusion
  - Aim Hb > 7 g/dl
- Platelet transfusion
  - Aim Plt > 50 x 10⁹/l or
  - If CNS bleed aim Plt > 100 x 10⁹/l

LIFE THREATENING OR UNCONTROLLED BLEED
- Contact Consultant Haematologist

Andexanet Alfa
- Contact Consultant Haematologist

Bleeding is uncontrolled

Factor Xa inhibitors: Management of haemorrhage and surgery
Written by: Dr Catherine Bagot and Cristina Coelho
Approved by: NHSGGC ADTC Medicines Utilisation Sub-Committee
Review Date: September 2023