Guideline 240FM.2

240FM.2 RIVAROXABAN AND APIXABAN: GUIDANCE FOR MANAGEMENT OF OVERDOSE, BLEEDING AND EMERGENCY/ELECTIVE SURGERY

Introduction
Rivaroxaban (Xarelto®) and apixaban (Eliquis®) are direct factor Xa inhibitors with a half-life of 12 - 14 hours.
Rivaroxaban and apixaban are eliminated by hepatic metabolism (about ⅔) and by renal excretion (about ⅓) and the AUC (area under the curve) is increased in renal impairment.
The major adverse effect of all anticoagulant medications is bleeding.

For quick reference please see flowcharts:
- Appendix 1: Rivaroxaban and Apixaban: Overdose Protocol
- Appendix 2: Rivaroxaban and Apixaban: Haemorrhage Protocol
- Appendix 3: Rivaroxaban and Apixaban: Emergency Surgery Protocol
- Appendix 4: Rivaroxaban and Apixaban: Elective Surgery Protocol

All patients
Check coagulation screen indicating time of last rivaroxaban and apixaban dose when requesting test. Always remember that there are many causes of abnormal clotting results unrelated to anticoagulant drugs.

<table>
<thead>
<tr>
<th>APTT</th>
<th>Sensitive to rivaroxaban and apixaban.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin Time (TT)</td>
<td>Not sensitive to rivaroxaban and apixaban - a high result may suggest the presence of dabigatran.</td>
</tr>
<tr>
<td>Prothrombin Time (PT/INR)</td>
<td>Sensitive to rivaroxaban and variable sensitivity to apixaban - a normal result suggests that rivaroxaban levels are very low. Remember that warfarin also increases the PT.</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Not affected by rivaroxaban and apixaban.</td>
</tr>
</tbody>
</table>

Check full blood count, renal function and electrolytes (including calcium).

No bleeding or minor bleeding
1. Omit rivaroxaban or apixaban until the bleeding stops, unless the risk of thrombosis is very high.
2. Local measures may be helpful.
3. Consider cause of bleeding.
4. For oral cavity bleeding also consider tranexamic acid 250 mg/5 ml (5%) mouthwash (unlicensed) – 10 ml 8 hourly.

Major/life-threatening haemorrhage (e.g. CNS/major GI)
1. Reduction of absorption: The administration of activated charcoal may be helpful in the event of an acute (<6 hours) overdose.
2. Fluid replacement: Maintain good urine output as rivaroxaban and apixaban are partly excreted renally.
3. Blood product transfusion: Aim for platelet count >50 x 10⁹/L or if CNS bleed >100 x 10⁹/L. Consider platelet transfusion particularly if patient on antiplatelet agents.
4. Consider antifibrinolytics: Tranexamic acid 500 mg – 1000 mg IV 8 hourly.
4. Reversal: There is currently no reversal agent or antidote for rivaroxaban or apixaban. The administration of clotting factors or vitamin K is NOT anticipated to be effective in reversing the effects of rivaroxaban or apixaban.

Haemodialfiltration is NOT likely to be effective in removing rivaroxaban or apixaban as both drugs are highly protein-bound.
5. Discuss with consultant haematologist for further advice.
   - Prothrombin complex concentrate (Beriplex®) has been shown to produce reversal of the effect of rivaroxaban in healthy volunteers but there is little data to support its use in acute bleeding. There is no clinical data for apixaban. See Guideline 191FM Protocol for Over-Anticoagulation with Warfarin (Appendix 1) for advice and reconstitution of Beriplex®.
Elective surgery

Pre-op

1. Check creatinine clearance to guide when to stop rivaroxaban and apixaban pre-operatively.
   Note that a creatinine clearance of less than 30 ml/min has relatively little influence on the half-life of rivaroxaban or apixaban, however the AUC is significantly increased in these patients.

Timing of interruption of rivaroxaban and apixaban prior to procedures or surgery

<table>
<thead>
<tr>
<th>Calculated creatinine clearance (ml/min)</th>
<th>Half-life (hours)</th>
<th>Timing of last dose before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>12 – 17</td>
<td>24 hours</td>
</tr>
<tr>
<td>&gt; 15 ≤ 30</td>
<td>16 – 18</td>
<td>2 days</td>
</tr>
</tbody>
</table>

* Standard risk procedures, e.g. cardiac catheterisation, ablation therapy, colonoscopy without removal of large polyps and uncomplicated laparoscopic procedures such as cholecystectomy.

‡ High risk procedures, e.g. insertion of pacemakers or defibrillators (resulting from the risk of pocket haematoma), large hernia surgery and major cancer/abdominal/spinal/urological/vascular surgery and neuroaxial anaesthesia.

2. Bridging therapy

   Generally, the rapid offset and onset of rivaroxaban and apixaban obviates the need for perioperative bridging therapy in many patients, but you must consider the risk of thrombosis very carefully: See Guideline 733FM Thromboprophylaxis in Adults.

Post-op: Restarting rivaroxaban and apixaban after surgery

General principles: The appropriate time to re-start rivaroxaban and apixaban after surgery will be determined by the bleeding risk of the surgery, the urgency for restarting thromboprophylaxis and the haemostatic state of the patient.

The anticoagulant onset of effect of rivaroxaban and apixaban is within 2 hours, provided that intestinal absorption is normal.

Caution is required when resuming rivaroxaban or apixaban, especially in those patients who have had surgery with a high bleeding risk. Re-start once complete haemostasis is achieved and renal function is stable. In patients having high bleeding risk surgery or procedures, it is sensible to delay resumption of rivaroxaban or apixaban for two to three days after such procedures.

Short term use of low molecular weight heparin (LMWH)/heparin may be appropriate where thromboprophylaxis is required but the risks from wound bleeding are increased or if a patient has a prolonged delay in resuming oral intake. The risk for thrombosis should be assessed. If a patient is on heparin after surgery and there is intent to restart rivaroxaban or apixaban, this should be done ≤ 2 hours prior to the time of the next scheduled dose of LMWH or at the time IV heparin is discontinued.

Post-operative resumption of rivaroxaban and apixaban

<table>
<thead>
<tr>
<th>Low bleeding risk</th>
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<tbody>
<tr>
<td>Resume on day after surgery (24 hours post-operative)*</td>
<td>Resume 2 - 3 days after surgery (48 - 72 hours post-operative)*</td>
</tr>
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</table>

*For those at high risk of thromboembolism, consider administering a reduced dose of rivaroxaban or apixaban on the evening after surgery and on the first post-operative day after surgery or bridging therapy with LMWH/heparin.
References


See also:

- Guideline 34FM Dabigatran: Guidance for Management of Overdose, Bleeding and Emergency/Elective Surgery
- Guideline 83FM Peri-operative Bridging of Warfarin Therapy in Adult Patients undergoing Elective Surgery or Invasive Procedures
- Guideline 84 Massive Transfusion (BHT users only)
- Guideline 191FM Protocol for Over-Anticoagulation with Warfarin
- Guideline 222 Adult and Paediatrics Injectables Guide (BHT users only)
- Guideline 313FM Dabigatran, Rivaroxaban, Edoxaban and Apixaban for Atrial Fibrillation
- Guideline 733FM Thromboprophylaxis in Adults

BHT Policy 071 – Unlicensed Medicines Policy (Annexe 4 of the Medicines Policy)
Appendix 1: Rivaroxaban and Apixaban Overdose Protocol

STOP RIVAROXABAN or APIXABAN

- Coagulation screen to include APTT and prothrombin time (PT)
- Document time of last dose of rivaroxaban or apixaban
- FBC and renal function (creatinine clearance)

- PT and/or APTT prolonged
  - Rivaroxaban and apixaban effect likely to be significant
  - (Consider oral activated charcoal if rivaroxaban and apixaban ingestion <6 hours)

Maintain BP and urine output

Is the patient bleeding?

Yes:
Refer to haemorrhage protocol - see appendix 2 and guideline 84 Massive Transfusion

No:
Monitor PT and APTT 12 hourly until normal.
Review need for oral anticoagulation.

PT and APTT normal: Rivaroxaban levels very low or absent. Some apixaban may be present.
Appendix 2: Rivaroxaban and Apixaban Haemorrhage Protocol

STOP RIVAROXABAN AND APIXABAN

- Coagulation screen to include APTT and prothrombin time (PT)
- Document time of last dose of rivaroxaban and apixaban
- FBC and renal function (creatinine clearance)

MINOR BLEED

- Mechanical compression
- Tranexamic acid
  - 500 mg – 1000 mg PO
  - Mouth wash for oral bleed
- Delay next rivaroxaban and apixaban dose or discontinue treatment

MAJOR BLEED*

- Optimise tissue oxygenation
- Control haemorrhage (mechanical compression/surgical intervention)
- Tranexamic acid 500 mg – 1000 mg IV 8 hourly
- Red cell transfusion
  - Aim for haemoglobin >70 g/l
- Platelet transfusion
  - Aim for platelets >50 x 10⁹/l or if CNS bleed aim for platelets >100 x 10⁹/l
- Contact on-call haematologist if contemplating use of prothrombin complex concentrate (PCC)

* Major bleed: Symptomatic bleeding in a critical organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome. (Schulman et al. J Thromb Haemost 2010; 3:692-694)
STOP RIVAROXABAN AND APIXABAN AND CONTACT SURGEON/ANAESTHETIST

- Coagulation screen to include APTT and prothrombin time (PT)
- Document time of last dose of rivaroxaban and apixaban
- FBC and renal function (creatinine clearance)

- APTT and/or PT prolonged
- Rivaroxaban or apixaban effect likely to be significant
- (Consider oral activated charcoal if rivaroxaban or apixaban ingestion <6 hours)

- APTT and PT normal: Rivaroxaban levels very low or absent. Some apixaban may be present.

Regional anaesthesia (spinal/epidural) is considered to be contraindicated.

Discuss with surgeon feasibility of delaying surgery

Surgical delay ≥12 hours

Refer to elective surgery guidance. Risk of bleeding dependent on:
- Time since last rivaroxaban and apixaban dose
- Type of surgery
- Renal function/eGFR

Surgery within 12 hours

- Contact on-call haematologist
- Consider prothrombin complex concentrate
Appendix 4: Rivaroxaban and Apixaban Elective Surgery Protocol

Pre-op

- Check creatinine clearance
- Assess bleeding risk of surgery

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Post-op

- Assess bleeding risk of surgery
- Assess haemostatic state of patient and renal function
- Is the patient tolerating oral diet?

Haemostasis achieved

- Patient is tolerating oral diet
- Patient unable to tolerate oral diet

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