Dear Colleagues

The following guidance has not been reviewed within the set timescale.

**Guidance On The Management Of Surgery, Other Invasive Procedures Or Major Haemorrhage In Patients Receiving One Of The New Oral Anticoagulants [Dabigatran, Rivaroxaban And Apixaban]**

Although this guidance is still available for use, please be advised however, that the content of this guidance may no longer be valid and its use should be risk assessed. This will remain the case until the lead author or those responsible for the guidance undertake its review.

If you have any queries regarding this please do not hesitate to contact the Pharmacy and Medicines Directorate.

Yours sincerely

Sandy Thomson
Interim Chair of Medicines Guidelines and Policies Group
Guidance On The Management Of Surgery, Other Invasive Procedures Or Major Haemorrhage In Patients Receiving One Of The New Oral Anticoagulants [Dabigatran, Rivaroxaban And Apixaban]

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Signature:

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Lead Author/Co-ordinator: Consultant Haematologist

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Purpose/description: This document is to provide guidance to clinicians dealing with patients who require discontinuation of dabigatran, apixaban or rivaroxaban prior to a surgical or other invasive procedure. It also provided guidance on the management of bleeding in patients taking these drugs

Responsibilities for implementation:

Organisational: CHP General manager/Clinical leads Acute Sector Operational Management Team and Acute Sector General Manager

Hospital/Interface services: Assistant General Managers and Group Clinical Directors

Operational Management Unit: Unit Operational Managers

Departmental: Clinical Leads

Area: Line Managers

Policy statement: It is the responsibility of supervisory staff at all levels to ensure that their staff are working to the most up to date and relevant policies, protocols procedures. By doing so, the quality of the services offered will be maintained, and the chances of staff making erroneous decisions which may affect patient, staff or visitor safety and comfort will be reduced.

Review: Review 2 yearly. Any significant changes in evidence will result in earlier alteration
This document is also available in large print and other formats and languages, upon request. Please call NHS Grampian Corporate Communications on (01224) 551116 or (01224) 552245.

Responsibilities for review of this document: Consultant Haematologist

Responsibilities for ensuring registration of this document on the NHS Grampian Information/ Document Silo: Medicines Management Pharmacist, Pharmacy and Medicines Directorate

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Guidance On The Management Of Surgery, Other Invasive Procedures Or Major Haemorrhage In Patients Receiving One Of The New Oral Anticoagulants [Dabigatran, Rivaroxaban And Apixaban]

1. Summary

- The new oral anticoagulants have short half lives (8-12 hours), although longer in patients with significant renal impairment. They are used for thromboprophylaxis in lower limb orthopaedic surgery and in subjects with atrial fibrillation and for treatment of venous thromboembolism.

- There is a poor correlation between routine coagulation tests, such as APPT and PT, and concentrations of these drugs in the plasma.

- For most elective procedures with a significant bleeding risk, omission of 1-4 days of anticoagulant treatment is required (see tables in Section 3).

- For procedures with a low bleeding risk, such as most dental surgery, it is likely that discontinuation is not required based on studies of patients taking warfarin where patients in therapeutic range did not benefit from discontinuation or reversal pre-operatively.

- Because the anticoagulant effect of these drugs may not be rapidly reversed or counteracted, management of emergency surgery or presentation with clinical bleeding is potentially challenging.

- At the present time there is limited evidence on which to base guidance for the above situations. The following advice is largely empirical with a pragmatic view towards balancing the thrombotic and haemorrhagic risks facing anticoagulated patients requiring invasive procedures or experiencing major bleeding.

- The general approach towards these situations is to:
  - Consider the risk of bleeding (patient and procedural) associated with not discontinuing anticoagulation.
  - Consider the thrombosis risk (indication for anticoagulation and procedural risk) associated with temporary discontinuation of anticoagulation.
2. Elective Minor Invasive Procedures

- Minor dental work (e.g. Prosthodontics, Conservation, Endodontics, Hygiene Phase Therapy and Orthodontics) may be undertaken without omitting any doses of anticoagulant. It is recommended that these procedures are undertaken at least 12 hours after the last dose of dabigatran or apixaban and 24 hours after the last dose of rivaroxaban (this corresponds with trough levels of the drug in circulation). In these patients the dose of anticoagulant that is due post procedure should be withheld for 2-4 hours post procedure and then administered as normal as long as there are no concerns around bleeding at that time. A local anaesthetic containing a vasoconstrictor should be used, unless contra-indicated. Where possible use an infiltration or intra-ligamentary injection. If there is no alternative and an inferior alveolar nerve block is used, the injection should be administered slowly using an aspirating technique.

- Invasive dental work (e.g. Extractions, Minor Oral Surgery, Periodontal Surgery and Biopsies), routine upper and lower gastrointestinal endoscopy +/- simple biopsy but excluding colonic polypectomy, joint injections and cataract extraction with lens implantation should be delayed until 24 hours after the last dose of dabigatran, rivaroxaban or apixaban. The next dose of anticoagulant should be deferred until 4 hours post procedure (or longer if haemostasis has not been achieved).

- If the patient has significant renal impairment (CrCl <50mL/min) the anticoagulant may have to be omitted for more than 24 hour pre-procedure and an assessment of anticoagulant status undertaken shortly pre-procedure. Local laboratory advice on interpretation of coagulation tests should be sought.
3. Elective Major Invasive Procedures

- The oral anticoagulants need to be discontinued prior to the procedure. The aim is to perform the surgery with low levels or no circulating anticoagulant. In most cases this will mean achieving a normal PT and APTT but these measures alone may not correlate with low drug levels in the circulation. In most cases pre-operative bridging therapy with LMWH should not be required. It should be remembered that dabigatran (if eGFR <30mL/min) and rivaroxaban and apixaban (if eGFR <15mL/min) are contra-indicated in patients with significant renal impairment.

**Dabigatran:** Patients will usually be receiving the drug twice daily. The duration for which the drug should be omitted prior to major surgery is dependent on renal function, as follows. For convenience the number of doses to be omitted has been cited as well as the number of days prior to the procedure for discontinuation:

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Estimated t/2 Hours (approx)</th>
<th>Omit dabigatran before surgery</th>
<th>Omit dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CrCl mL/min</strong></td>
<td><strong>Estimated t/2 Hours (approx)</strong></td>
<td><strong>Omit dabigatran before surgery</strong></td>
<td><strong>Omit dabigatran before surgery</strong></td>
</tr>
<tr>
<td>≥ 80</td>
<td>13</td>
<td>2 days before</td>
<td>1 day before</td>
</tr>
<tr>
<td>≥50 &lt; 80</td>
<td>15</td>
<td>2-3 days before</td>
<td>1-2 days before</td>
</tr>
<tr>
<td>≥30 &lt;50</td>
<td>18</td>
<td>4-6 days before</td>
<td>2-4 days before</td>
</tr>
</tbody>
</table>

**Rivaroxaban:** Patients will usually be receiving the drug once daily except in the first 3 weeks after acute venous thromboembolism. The number of days and doses of the drug based on a once daily (usual) dosing regimen are as follows. If the patient has significant renal impairment [eGFR < 30mL/min] advice should be sought.

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Estimated t/2 Hours (approx)</th>
<th>Omit rivaroxaban before surgery</th>
<th>Omit rivaroxaban before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CrCl mL/min</strong></td>
<td><strong>Estimated t/2 Hours (approx)</strong></td>
<td><strong>Omit rivaroxaban before surgery</strong></td>
<td><strong>Omit rivaroxaban before surgery</strong></td>
</tr>
<tr>
<td>≥ 50</td>
<td>8-9</td>
<td>2 days before</td>
<td>1 day before</td>
</tr>
<tr>
<td>≥30 &lt;50</td>
<td>9</td>
<td>2 days before</td>
<td>1 day before</td>
</tr>
<tr>
<td>≥15 &lt;30</td>
<td>9-10</td>
<td>3 days before</td>
<td>2 days before</td>
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**Major surgery, high bleeding risk or where any increased bleeding is unacceptable**

**Non-major surgery and low bleeding risk**
**Apixaban**: Patients will normally be taking the drug twice daily. There is dose reduction for patients with renal impairment when using this drug and it will not be used in patients with Cr Cl of < 15mL/min. The number of days and doses of the drug based on a twice daily (usual) dosing regimen are as follows. If the patient has significant renal impairment [eGFR < 30mL/min] advice should be sought.

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Estimated t/2 Hours (approx)</th>
<th>Omit apixaban before surgery</th>
<th>Omit apixaban before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl mL/min</td>
<td></td>
<td><strong>Major surgery, high bleeding risk or where any increased bleeding is unacceptable</strong></td>
<td><strong>Non-major surgery and low bleeding risk</strong></td>
</tr>
<tr>
<td>CrCl &gt;50</td>
<td>7-8</td>
<td>2 days before 4 doses</td>
<td>1 day before 2 doses</td>
</tr>
<tr>
<td>CrCl 30-50</td>
<td>17-18</td>
<td>3 days before 6 doses</td>
<td>2 days before 4 doses</td>
</tr>
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</table>

**Post-operative** thromboprophylaxis will be most simply achieved with LMWH at prophylactic doses. The re-introduction of any anticoagulant should follow clinical assessment of bleeding and bleeding risk 4-12 hours post-surgery. These anticoagulants have a similar rapid onset of action – around two hours. Prophylactic doses of dabigatran, rivaroxaban and apixaban can be considered here if it is felt desirable to re-commence the patient on the anticoagulant that they are going to receive long-term. The escalation from prophylactic doses to therapeutic doses is dependent on consideration of the thrombosis and bleeding risk. If LMWH is used initially, the patient can re-start rivaroxaban, apixaban or dabigatran 24 hours after the last dose.

4. **Major Haemorrhage and Emergency Invasive Procedures**

There is no specific antidote for dabigatran, rivaroxaban or apixaban. The key principles in managing these situations are:

- Assess coagulation screen and renal function bearing in mind the limited prolongation of PT and APTT induced by therapeutic doses of dabigatran, rivaroxaban and apixaban.

- Ascertain time of the most recent dose of anticoagulant, and administer no further doses. If very recent ingestion (≤ 2h for dabigatran and rivaroxaban and ≤ 6 hours for apixaban), consider administration of oral activated charcoal to inhibit absorption.

- If significant dabigatran effect, as assessed by coagulation screen (e.g. APTT ratio >2.0 and a prolonged TT), consider feasibility of urgent haemodialysis to remove anticoagulant. Rivaroxaban and apixaban are highly protein bound and so dialysis is ineffective.
• Consider possibility of delaying major surgery until the anticoagulant effect has sufficiently dissipated.

• If major surgery has to proceed in the face of significant anticoagulant effect:
  ❖ Ensure haemostatic platelet count and fibrinogen level and satisfactory pre-op Hb.
  ❖ Treat any additional causes of coagulopathy.
  ❖ Consider general haemostatic measures (e.g. 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 25-50mg/Kg) or activated clotting factors (e.g. Feiba 50 units/Kg).

• In the presence of major bleeding:
  ❖ Follow general major haemorrhage protocol – see separate algorithms for dabigatran, rivaroxaban and apixaban-treated patients (Appendices 1-3).

• Once haemostasis is secured and/or the invasive procedure completed introduce thromboprophylaxis with LMWH when appropriate. If dabigatran, rivaroxaban or apixaban is to be re-introduced this should be deferred until 24 hours after the last dose of LMWH.
Appendix 1 Management Of Bleeding In Patients Taking Dabigatran

- Stop dabigatran
  - Check FBC, PT, APTT and TCT
  - Check GFR/renal function

APTT (and TCT) prolonged OR APTT normal and TCT prolonged

Dabigatran effect may be present
  - Administer oral charcoal if within 2 hours of ingestion

Minor Bleed
- Mechanical Compression
- Tranexamic Acid PO 25mg/kg OR
- Tranexamic Acid IV 10 mg/kg
- Delay or withhold next dose dabigatran

Major Bleed
- Contact Haematologist*
  - Maintain blood pressure and urine output
  - Control bleeding by surgical or radiological means
    - Tranexamic acid 1 g IV
    - Consider red cell and platelet transfusion
    - Consider Beriplex 50 units/kg IV
    - Consider haemodialysis

No dabigatran effect present

*Consider Haemoclot assay for more accurate assessment of dabigatran levels
Appendix 2 Management Of Bleeding In Patients Taking Rivaroxaban

- Check FBC, PT, APTT and TCT
- Check GFR/renal function
- Stop rivaroxaban

PT prolonged
- Likely that there is a significant rivaroxaban effect
  - Administer oral charcoal if within 2 hours of ingestion

PT normal
- Unlikely that there is a significant rivaroxaban effect but be guided the time since drug ingestion

Minor Bleed
- Mechanical Compression
- Tranexamic Acid PO 25mg/kg OR
- Tranexamic Acid IV 10 mg/kg
- Delay or withhold next dose rivaroxaban

Major Bleed
- Contact Haematologist*
- Maintain blood pressure and urine output
- Control bleeding by surgical or radiological means
- Tranexamic acid 1 g IV
- Consider red cell and platelet transfusion
- Consider Beriplex 50 units/kg IV

*Consider accurate determination of rivaroxaban levels by anti-Xa assay
Appendix 3 Management Of Bleeding In Patients Taking Apixaban

Check FBC, PT, APTT and TCT
Check GFR/renal function
Stop apixaban

PT prolonged
Likely that there is a significant apixaban effect
Administer oral charcoal if within 6 hours of ingestion

Minor Bleed
- Mechanical Compression
- Tranexamic Acid PO 25mg/kg OR
- Tranexamic Acid IV 10 mg/kg
- Delay or withhold next dose apixaban

PT normal
Still possible that there is a significant apixaban effect be guided by time since drug ingestion

Major Bleed
- Contact Haematologist*
  - Maintain blood pressure and urine output
  - Control bleeding by surgical or radiological means
  - Tranexamic acid 1 g IV
  - Consider red cell and platelet transfusion
  - Beriplex 50 units/kg IV

*Consider accurate determination of apixaban levels by anti-Xa assay or PICT assay