Low Molecular Weight Heparin and Warfarin or Rivaroxaban for the Treatment of Deep Vein Thrombosis

Rivaroxaban is a new oral anticoagulant which works by the inhibition of the clotting factor Xa. Its main advantages over warfarin is its immediate action, negating the need for low molecular weight heparin (LMWH), and its dependable pharmacokinetics meaning drug monitoring and dose adjustment is not required. The evidence for its use comes from two studies which demonstrated broadly equal efficacy between rivaroxaban and the current standard of care [LMWH converting to a vitamin K antagonist (VKA)]:

- **Treatment of acute deep vein thrombosis (DVT).** The Einstein DVT study\(^1\) randomised patients between rivaroxaban (15mg twice daily for 3 weeks then 20mg daily) or LMWH/VKA. Treatment length was at the physician’s discretion but ranged from 3-12 months. The primary efficacy outcome (recurrent thrombosis) and primary safety outcome (major or clinically relevant bleeding) was no different between the groups [recurrent thrombosis rivaroxaban 36/1731 (2.1%) versus LMWH/VKA 51/1718 (3.0%), bleeding 8.1% in both groups]. Based on the study this drug has been licensed and NICE approved for this indication.

  A further part of the study (Einstein-Extend) randomised patients who had finished treatment in either arm to 6 or 12 months of rivaroxaban or placebo. Those in the rivaroxaban arm had fewer recurrent thrombosis [8/602 (1.3%) versus 42/594 (7.1%), number needed to treat 17] but a trend to more haemorrhage (4 versus 0).

- **Treatment of acute pulmonary embolism (PE).** The Einstein PE study\(^2\) randomised patients between rivaroxaban (15mg twice daily for 3 weeks then 20mg daily) or LMWH/VKA. Treatment length was at the physician’s discretion but ranged from 3-12 months. Primary efficacy outcome was recurrent thromboembolic events with primary safety outcomes being major bleeding and clinically significant bleeding.

  Fifty (2.1%) patients in the rivaroxaban arm and 44 (1.8%) in the LMWH/VKA arm suffered a thromboembolic event, this was statistically non-inferior. Major or clinically relevant bleeding was similar in both groups (10% versus 11.4%) but with fewer major haemorrhages in the rivaroxaban group [26/2381 (1%) versus 52/2444 (2%), number needed to treat 97]. The drug is awaiting licensing for this indication.

It is still unclear how representative these populations are, there has been no confirmatory studies or studies of long-term use published. The mean age in the DVT study was 55.8/16.4 years, so few elderly patients. There were only a couple of patients who had a creatinine clearance of less than 30mls/min. Rates of stopping the drug were similar in both arms. The time in therapeutic range for the VKAs was low (55.7%) compared to our average (68%) which may make it a poorer comparator.
Suggested recommendations for the use of rivaroxaban in treating DVT in Worcestershire

The NICE single technology assessment reviewed and approved rivaroxaban for the treatment of DVT. It is still unclear who will most benefit from rivaroxaban but the following is a guide:

Rivaroxaban should be considered in:
- Patients on long-term warfarin who have poor control (time in therapeutic range less than 55%) which is felt not be due to compliance issues.
- Patients with other medical conditions that require regular introductions of medications which interfere with warfarin, e.g. COPD with antibiotics, and cause the need for very frequent INR monitoring/dose changes.
- Patients who are currently managed on LMWH because of difficulty in INR monitoring.
- Patients with poor mobility who find it difficult to attend outpatient clinics and/or require home visits.

Rivaroxaban should be used in caution in patients with:
- Renal dysfunction
- Aged more than 75 years
- Patients who are to be started on anticoagulation indefinitely because of the lack of long-term safety data for rivaroxaban.

Rivaroxaban should not be used in the following situations:
- Patients who are already on warfarin and well controlled, and who have not had adverse events. This is due to the lack of long-term safety data in this indication.
- History of gastrointestinal bleed
- Pregnancy or lactation
- Patients with cancer
- Patients with known antiphospholipid syndrome
- Patients with a target INR more than 3.0
- Other indications for warfarin, except non-valvular atrial fibrillation
- Patients with known poor compliance, given the short half life of rivaroxaban missing a dose can leave a patient not anticoagulated for considerable periods of time.

Rivaroxaban is suggested as an option which should be discussed with the patient in:
- Patients who have a suspected DVT and are awaiting appropriate imaging.
- Patients who have had a provoked DVT or first unprovoked DVT in whom a finite period of anticoagulation is required.

Prescribing of rivaroxaban: Local algorithm available
Full details are available from the SPC
(http://www.medicines.org.uk/EMC/medicine/25586/SPC/Xarelto%2020mg%20film-coated%20tablets/)

New patients:
- Check FBC and coagulation screen, if low platelets or abnormal coagulation discuss with haematology.
- Check U&E – suggest avoiding if GFR less than 30mls/min
- Start rivaroxaban at 15mg twice daily for 3 weeks then 20mg daily
- Suggest monitoring U&E every year if baseline normal, every six months if baseline abnormal. No requirement for coagulation monitoring.

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Patients on warfarin

- Check U&E – suggest avoiding if GFR less than 30mls/min
- Stop warfarin and monitor INR daily, start rivaroxaban when INR less than 2.5
- Suggest monitoring U&E every year if baseline normal, every six months if baseline abnormal. No requirement for coagulation monitoring.

Patients on LMWH

- Check U&E – suggest avoiding if GFR less than 30mls/min
- Stop LMWH and start rivaroxaban between 0-2 hours before next dose would have been due.
- Suggest monitoring U&E every year if baseline normal, every six months if baseline abnormal. No requirement for coagulation monitoring.

RIVAROXABAN WILL CAUSE PROLONGATION OF THE COAGULATION SCREEN

Management of patients having operative procedures

If at all possible the operation should be delayed for as long after the thrombosis as possible. Rivaroxaban has a half life of approximately 5-13 hours, but this extends in patients with renal impairment and the elderly. A normal coagulation profile may indicate that the anticoagulant effect of the drug has worn off.

Discontinuation is advised as below:

<table>
<thead>
<tr>
<th>Renal function (CrCl) (ml/min)</th>
<th>Increase in rivaroxaban concentration</th>
<th>Timing of last dose prior to surgery</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard risk of bleeding</td>
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<tr>
<td></td>
<td></td>
<td>High risk of bleeding</td>
</tr>
<tr>
<td>More than 80</td>
<td>1.0x</td>
<td>24 hours</td>
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<tr>
<td>80-50</td>
<td>1.4x</td>
<td>2 days</td>
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<tr>
<td>30-50</td>
<td>1.5x</td>
<td>3 days</td>
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<td>Less than 30</td>
<td>1.6x</td>
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Epidural and spinal anaesthesia may require a longer time from last dose. The drug can usually be restarted the following day when complete haemostasis has been secured but if there is concern over bleeding then re-introduction should be delayed, bridging therapy with LMWH may be required if there is a more than 24 hour delay.

Management of bleeding on rivaroxaban

Where there is minor bleeding then the next dose of rivaroxaban should be withheld and local measures taken to stop the bleeding.

Moderate and severe bleeding should be treated with local measures, early surgical/radiological interventions, blood product support (blood bank must be informed of a patient bleeding on rivaroxaban).

Life, limb or sight threatening bleeding should be treated as severe bleeding but the use of recombinant activated factor VIIa (NovoSeven®) or prothrombin complex concentrate should also be considered.

Consideration should be given to the use of tranexamic acid in all bleeding patients (contra-indicated in urinary tract bleeding).

Emergency surgery on rivaroxaban

If a patient requires emergency surgery a PT and APTT should be performed; if this is normal there is no residual activity of rivaroxaban and the operation can go ahead as normal. If it is prolonged the operation should be delayed as long as possible to allow drug levels to fall. If the patient requires the operation with a prolonged PT and APTT then the blood bank should be informed. The operation should proceed; if there is bleeding then standard blood product support should be used. If there is major non-surgical bleeding then

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consideration should be given for the use of prothrombin complex concentrate (Beriplex®) and recombinant factor VIIa (NovoSeven®). There is no role for pre-operative or prophylactic blood products.

**Dental procedures on rivaroxaban**

Rivaroxaban at standard dose is approximately equitant to an INR of 2.5. Therefore dental procedures that previously would have been safely performed whilst on warfarin can be performed without interruption of rivaroxaban. It is reasonable to schedule the surgery as long after the rivaroxaban as possible to achieve lowest drug levels during the time of operation and to avoid having the next dose for 4 hours after the procedure.

**References**