DVT/PE Management with Rivaroxaban (Xarelto)

Rivaroxaban is FDA approved for the acute treatment of DVT and PE and reduction in risk of recurrence of DVT and PE.

FDA approved indications:
- Non-valvular atrial fibrillation, as an alternative to warfarin, for stroke prevention.
- Treatment of DVT and PE and reduction in risk of recurrence of DVT and PE.
- Prophylaxis of DVT following hip and knee replacement.

About the drug:
- Mechanism of action – Factor Xa inhibitor.
- Rapid absorption and peak activity in 2 – 4 hours
- Half-life 5 - 9 hours, in the elderly half-life is 11 – 13 hours.
- The drug will accumulate in renal and liver impairment.
- There are a limited number of drugs that may affect rivaroxaban levels
  Drug interactions include ketoconazole, itraconazole, ritonavir, carbamazepine, phenytoin, and rifampin (medications with combined P-gp and strong CYP3A4 interactions). Please see package insert for details.
- Higher doses (15- 20 mg tablets) should be taken with food, and lower doses (10mg tablets) may be taken with or without food.

Contraindications
- Bleeding or falls risks.
- Renal impairment, contraindicated in:
  - Atrial fibrillation with CrCl < 15 mL/min (need lower dose in CrCl 15 – 50mL/min)
  - DVT and PE with CrCl < 30 mL/min
  - DVT prophylaxis with CrCl < 30 mL/min
- Liver impairment - Child-Pugh B and C
- It has not been studied in pregnancy, but it does cross the placenta in animals

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and is excreted in rat milk.

- It has not been studied in valvular heart disease.

**Precautions**
- Anti-platelet agents increase the risk for hemorrhage – we advise that anti-platelet agents be stopped when taking rivaroxaban, unless there is a good reason to continue them.
- It should not be used together with other anticoagulants, like heparin or LMWH.

**Laboratory testing to be done prior to starting rivaroxaban**
- Baseline labs prior to starting rivaroxaban: CBC, Platelets, LFTs, SCr, INR and aPTT – results within 1 month are acceptable
- Routine monitoring is not required.
- Routine coagulation monitoring is not required. Liver and renal function should checked yearly, or more often, if clinically indicated.

**Dosing for DVT/pulmonary embolism**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Time after acute thrombosis</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT/pulmonary embolism</td>
<td>First 21 days following the acute event</td>
<td>15 mg bid</td>
</tr>
<tr>
<td></td>
<td>After 21 days</td>
<td>20 mg daily</td>
</tr>
</tbody>
</table>

**MAKE SURE THE DOSE IS CHANGED AFTER 21 DAYS**

The minimum duration of treatment is 3 months, with some patients needing treatment for longer periods, per ACCP guidelines, Chest 2012;141;e419S-e494S.

If rivaroxaban dose is delayed start alternative anticoagulant (e.g LMWH) ASAP after diagnosis is made.

**Dosing for other indications**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Renal function (CrCl mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>≥50</td>
<td>20 mg daily</td>
</tr>
<tr>
<td></td>
<td>15 – 49</td>
<td>15 mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt; 15</td>
<td>Do not use</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>≥30</td>
<td>Hip replacement 10mg daily for 35 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Knee replacement 10mg daily for 12 days</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>Do not use</td>
</tr>
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</table>
Who is not an appropriate candidate for rivaroxaban?

- Renal impairment, contraindicated in:
  - Atrial fibrillation with CrCl < 15 mL/min (need a lower dose for CrCl 15 – 50 mL/min)
  - DVT and PE with CrCl < 30 mL/min
  - DVT prophylaxis with CrCl < 30 mL/min
- Liver impairment - contraindicated in Child-Pugh B and C.
- Patient concerns about higher drug costs. Most members will pay a higher brand co-pay for rivaroxaban and a lower generic co-pay for warfarin.
- If a patient is well controlled on warfarin, consider leaving them on warfarin
- If patient has significant risks for bleeding and anticoagulation is given on a trial basis we would recommend use of shorter acting reversible agents for initial therapy. This may require inpatient monitoring.

Side effects

- The risk of bleeding appears similar to other anticoagulants.
  - DVT and PE treatment – any bleeding was similar (28.0-28.3%). Clinically relevant non-major bleeding was similar (8.6-8.7%). Major bleeding was numerically less with rivaroxaban (1.0% vs 1.7%).
  - Atrial fibrillation – major bleeding was similar (3.5-3.6 events per 100 patient-years).
  - DVT prophylaxis following knee or hip replacement surgery - major bleeding was similar (0.2-0.3%).
- Other adverse reactions include upper abdominal pain, dyspepsia, back pain, and oropharyngeal pain.

How rivaroxaban affects laboratory studies

- Rivaroxaban prolongs the PTT and INR and the Anti-Factor Xa test is also influenced by the drug.
- The Anti- Factor Xa test can be used to evaluate plasma levels, but appropriate calibration is not available to check for presence of rivaroxaban or drug levels.
- Tests that will not be reliable on rivaroxaban include lupus anticoagulant testing, Factor X chromogenic, Protein S activity and clotting factor activities. Testing for Protein C, antithrombin and fibrinogen activity should be accurate on rivaroxaban.

Perioperative management

Holding rivaroxaban prior to the procedure:

- **Bleeding risk low:**
  - CrCl ≥ 50 mL/min - hold for 24 hours prior to procedures
  - CrCl < 50 mL/min - hold for 48 hours prior to procedures
- **Bleeding risk high:**
  - CrCl ≥50 mL/min - hold for 48 hours prior to procedures
  - CrCl < 50 mL/min - hold for 72 hours prior to procedures

Restarting after a procedure:

- Timing of resumption of therapeutic-dose rivaroxaban must be adjusted according to bleeding risk - restart the drug 24 – 72 hours after a procedure.
NOTES:
- The anticoagulant effect occurs within 2 – 4 hours after drug ingestion.
- If a patient is high risk for recurrent DVT/PE and rivaroxaban has to be discontinued for reasons other than bleeding another anticoagulant should be given.
- In patients on rivaroxaban for non-valvular atrial fibrillation discontinuation of rivaroxaban resulted in an increased rate of stroke. If rivaroxaban has to be discontinued for reasons other than bleeding another anticoagulant should be given.

Converting from or to warfarin

Converting from warfarin:
- If the patient is well controlled on warfarin consider staying on warfarin.
- Do not change anticoagulation within a month of the acute thrombotic event as the dose to use is unclear.
- If the patient is > 1 month from an acute thrombotic event, standard dosing of rivaroxaban (20mg daily) is recommended.

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These are the procedures to use in the conversion:
- The package insert recommends starting rivaroxaban when the INR is below 3.
- A more conservative approach, that we recommend, is:
  - INR < 2 - start rivaroxaban that day.
  - INR 2 – 2.5 – hold warfarin and start rivaroxaban the next day.
  - INR > 2.5 - hold warfarin, monitor INR daily and start rivaroxaban per recommendations above.

Converting to warfarin:
- The INR, Factor X and Factor II activity and Factor X chromogenic will not be reliable on rivaroxaban.
- Rivaroxaban will prolong the INR

The procedure we recommend is:
- Stop rivaroxaban
- Start lovenox when the next dose of rivaroxaban is due and start warfarin with INR monitoring

Converting from or to Parenteral Anticoagulants
- For patients currently receiving a parenteral anticoagulant, start rivaroxaban 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g. intravenous unfractionated heparin).
- For patients currently taking rivaroxaban, give the dose of the new drug at the time rivaroxaban would have been taken.

Guidelines for the Management of Bleeding

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• There is no specific agent to reverse the drug.
• Plasma will not work as the drug will inhibit Factor X in transfused plasma.
• Rivaroxaban is not dialyzable.
• There is very little data to help guide us in managing bleeding complications on the drug.

**Lab testing**

• CBC, Platelet count, serum creatinine, LFT, aPTT, INR, and fibrinogen activity.
• Repeat testing every 4 hours until bleeding has stopped

**Note:** INR and PTT will be abnormal on rivaroxaban

**For minor bleeding**

• Stopping the drug will decrease the bleeding risk. Decisions about stopping can be based on the risk of stroke and the severity of the bleeding. Factors to consider include the duration of the drug effects (1-2 days in patients with normal renal function) and the onset of action when restarting (peak activity within 2-4 hours).
• Use local measures to control the site bleeding
• Keep hydrated
• Replace fluids and blood products as needed

**For severe or life-threatening bleeding**

• Stop the drug
• Control of bleeding site and supportive care of patient
• Activated charcoal administered if the drug has been given within 2 hours.
• Blood transfusion
  1. Transfuse RBCs to keep Hgb above 9 or 10
  2. After the 4th unit of RBCs start giving RBCs and Plasma on a 1:1 ratio (to avoid a dilutional coagulopathy)
  3. Cryoprecipitate, give 10 units after the 8th unit of RBCs, 4th unit of Plasma – May not need cryo if fibrinogen activity is > 100 mg/dl
• Recombinant activated Factor VII - one dose 1 mg if <100 kg and 2 mg if > 100 kg. This should be considered if bleeding is life-threatening.

**Note:** Recombinant activated Factor VII and prothrombin complex concentrates have not been evaluated for reversal of bleeding in humans.

**Disclaimer:** I have included recombinant activated Factor VII (rFVIIa) as an option to help with clot formation at the site of bleeding. It does not reverse the drug and the correct dose is unknown. Thrombosis is a potential side effect of rFVIIa.

Dr. Colleen Morton.

**References:**

3. Xarelto prescribing information,

Questions: Please reply to this e-mail, and your questions(s) will be directed to the authors of this Pearl, Bruce Burnett, MD, Peter Marshall, PharmD, and Colleen Morton, MD.

Pearls of Knowledge Archive

All Pearl recommendations are consistent with professional society guidelines, and reviewed by HealthPartners Physician Leadership.