Rivaroxaban monograph

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Introduction

Rivaroxaban is an orally active direct factor Xa inhibitor manufactured by Bayer; it is marketed as Xarelto. Rivaroxaban is a novel oral anticoagulant (NOAC) that received initial FDA approval in 2011 for thromboprophylaxis in patients with nonvalvular atrial fibrillation and for the prophylaxis of DVT in patients undergoing knee or hip replacement surgery. In November 2012, the FDA expanded the use of rivaroxaban to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) and to reduce the recurrence of DVT/PE. Since rivaroxaban was the first agent approved for prophylaxis and treatment of DVT/PE, it has the longest record for these indications compared to the other two NOACs (dabigatran and apixaban).

This monograph does not provide detailed rivaroxaban prescribing information. This can be found in the FDA prescribing. Instead, we attempt to summarize the important points from clinical trials and updates.

1. Indication and dosage

Nonvalvular atrial fibrillation: 20 mg once daily with the evening meal. From the ROCKET AF trial, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism. There was no difference in the risk of major bleeding. However, intracranial and fatal bleeding occurred less frequently with rivaroxaban. Of note, rivaroxaban was superior to warfarin in patients receiving at least one dose of a study drug who were followed for events during treatment (as-treated population). However, there was no significant difference in superiority analysis in the intention-to-treat population.[1]

Acute symptomatic DVT: 15 mg twice daily for 3 weeks, followed by 20 mg once daily for 3, 6, or 12 months. From the EINSTEIN-DVT trial, rivaroxaban had non-inferior efficacy with respect to the primary outcome (recurrent venous thromboembolism) compared to enoxaparin and vitamin K antagonist. There was no difference in the risk of major bleeding or in clinically relevant nonmajor bleeding.[2]

Acute symptomatic PE: 15 mg twice daily for 3 weeks, followed by 20 mg once daily for 3, 6, or 12 months. From the EINSTEIN-PE trial, rivaroxaban was non-inferior to enoxaparin and vitamin K antagonist for the primary efficacy outcome of symptomatic recurrent venous thromboembolism. There was less major bleeding in the rivaroxaban group.[3]

Extended anticoagulation for symptomatic deep vein thrombosis or pulmonary embolism after completion of 6 to 12 months of treatment: 20 mg once daily for an additional 6 or 12 months. From the EINSTEIN-Extension trial, rivaroxaban was superior to placebo for preventing recurrent venous thromboembolic events. There was no difference in major bleeding, although increased risk of clinically relevant nonmajor bleeding in the rivaroxaban group was seen.[2]

Thromboprophylaxis after total hip arthroplasty: 10 mg once daily, start 6 to 8 hours after wound closure, for 35 days. From the RECORD1 trial, rivaroxaban was more effective than enoxaparin with similar safety profiles.[4] From the RECORD2 trial, rivaroxaban 10 mg once daily for 31-39 days was more

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DOI: 10.12746/swrccc2015.0310.130

effective than enoxaparin 40 mg once daily for 10-14 days for the prevention of venous thromboembolism with similar bleeding risk.[5]

Thromboprophylaxis after total knee arthroplasty: 10 mg once daily, beginning 6 to 8 hours after surgery, for 10-14 days. Rivaroxaban was superior to enoxaparin for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding.[6]

Secondary prevention after acute coronary syndrome (Approved by European Medicine Agency, but not by the FDA): 2.5 mg twice daily (co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine). From the ATLAS ACS2-TIMI 51 trial, rivaroxaban had 1.6% absolute risk reduction of the composite end point of death from cardiovascular causes, myocardial infarction or stroke (number need to treat of 63). Although rivaroxaban did not increase risk of fatal bleeding, it increased risk of major bleeding, bleeding requiring medical attention or intracranial hemorrhage by 6.8% (number need to harm of 15).[7]

2. Administration

2.1) Switching to and from rivaroxaban[8]

Conversion from warfarin: Discontinue warfarin and initiate rivaroxaban as soon as INR falls to <3.0.

Conversion to warfarin: Initiate warfarin and a parenteral anticoagulant 24 hours after discontinuation of rivaroxaban.

Conversion from continuous infusion unfractionated heparin: Initiate rivaroxaban at the time of heparin discontinuation.

Conversion to continuous infusion unfractionated heparin: Initiate continuous infusion unfractionated heparin 24 hours after discontinuation of rivaroxaban

Conversion from anticoagulants (other than warfarin and continuous infusion unfractionated heparin): Discontinue current anticoagulant and initiate rivaroxaban ≤2 hours prior to the next regularly scheduled evening dose of the discontinued anticoagulant.

Conversion to other anticoagulants (other than warfarin): Initiate the anticoagulant 24 hours after discontinuation of rivaroxaban.

2.2) Discontinuation for surgery and other interventions

Rivaroxaban should be stopped at least 24 hours before the procedure and should be restarted after the procedure as soon as adequate hemostasis has been established. The discontinuation period prior to surgery should be longer if the patient has impaired kidney function and in elderly patients due to impaired clearance and a longer half-life of the medication.[9]

2.3) Administration options

For patients who are unable to swallow whole tablets, rivaroxaban tablets may be crushed and mixed with apple sauce or suspended in 50 mL of water and administered within 4 hours. Avoid administration of rivaroxaban distal to the stomach because this can result in reduced absorption.

3. Dose adjustments

3.1) Renal impairment[8]

Nonvalvular atrial fibrillation

CrCl > 50 mL/min – No dose adjustment needed.
CrCl 30-50 mL/min – 15 mg once daily
CrCl15-30 mL/min – Not studied but 15 mg once daily was expected to result in serum concentrations similar to those with normal renal function[10-13]
CrCl <15 mL/min – Avoid use

Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and PE

CrCl >30 mL/min – No dose adjustment needed.
CrCl <30 mL/min – Avoid use since these patients were excluded from the studies.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery[4-6]

CrCl >30 mL/min – No dose adjustment needed.
CrCl <30 mL/min – Avoid use

3.2) Hepatic impairment: Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.[8] All of the randomized studies excluded patients who have clinically significant liver disease (e.g., acute hepatitis, chronic active hepatitis, or cirrhosis) or an alanine aminotransferase level that was three times the upper limit of normal range or higher.[1-6]

3.3) Body weight, age, gender, or ethnicity: No dose adjustment needed.[14-18]

4. Contraindications[8]

- Active pathological bleeding
- Severe hypersensitivity reaction to rivaroxaban

5. Precaution and warning

5.1) Increased risk of thrombotic events after premature discontinuation

After sites were notified to end study treatment, 92.2% of patients in both groups still on the assigned study drug were transitioned to VKAs. The median times to reach therapeutic INR were13 days for those previously assigned to rivaroxaban versus 3 days for the warfarin group. Patients transitioning from rivaroxaban to warfarin developed more primary events during the first month after termination of randomized treatment compared to patients who were assigned for VKAs (22 vs. 7; P=0.008). (appendix ROCKET AF trial)

5.2) Risk of bleeding

Rivaroxaban increases the risk of bleeding and can cause serious or fatal bleeding.

Concomitant use of other drugs that impair hemostasis increase the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy and non-steroidal anti-inflammatory drugs (NSAIDs).

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) increase rivaroxaban exposure and may increase bleeding risk.[8]

5.3) Spinal/epidural anesthesia or puncture

When spinal or epidural anesthesia is used or spinal puncture is employed, patients treated with rivaroxaban are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

To reduce the potential risk of bleeding, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An epidural catheter should not be removed earlier than 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of rivaroxaban is to be delayed for 24 hours.[8]

5.4) Patients with prosthetic heart valves

The safety and efficacy of rivaroxaban has not been studied in patients with prosthetic heart valves. Therefore, the use of rivaroxaban is not recommended in these patients.

5.5) Acute pulmonary embolism in hemodynamically unstable patients or in patients who may receive thrombolysis or pulmonary embolectomy

Initiation of rivaroxaban is not recommended acutely as an alternative to unfractionated heparin[3,8].

6. Reversal of bleeding

Discontinue rivaroxaban in patients with active pathological hemorrhage. The elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years. A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Partial reversal of prothrombin time prolongation has been seen after administration of a single bolus of 50 IU/kg prothrombin complex concentrates (PCC, Cofact) in healthy volunteers.[19,20] The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rF-VIIa) has not been evaluated.[8]

Xarelto announced on January 2015 that a phase 3 study testing the safety and efficacy of the antidote met its primary end point. In the trial, an 800 mg intravenous bolus of Andexanet alfa, which was tested in 41 healthy volunteers treated with rivaroxaban 20 mg for 4 days and then subsequently randomized to the study drug or placebo, “immediately and significantly” reversed the steady-state anticoagulation activity of rivaroxaban.[21]

The full results of the study, known as ANNEXA-R, were scheduled for presentation on Monday, March 16, 2015 at the American College of Cardiology 2015 Scientific Sessions.

7. Adverse reaction

The most common adverse reactions (>5%) was bleeding. Also seen was an increased risk of stroke after discontinuation in nonvalvular atrial fibrillation.

- In the ROCKET AF trial, the incidence of major bleeding from rivaroxaban was similar to warfarin at 3.6% and 3.4% per year, respectively (p=0.58). Rates of intracranial hemorrhage were significantly lower in the rivaroxaban group compared to warfarin (0.5% vs. 0.7% per year; HR, 0.67; 95% CI, 0.47 to 0.93; p=0.02). But major bleeding from gastrointestinal sites was more common in rivaroxaban group (3.2% vs. 2.2% per year, p=<0001).[1]

- In the treatment of symptomatic pulmonary embolism study, the incidence of major bleeding was lower in rivaroxaban compared to warfarin group (1.1% vs. 2.2%; HR, 0.49; 95% CI 0.31 to 0.79; p= 0.03).[3]

- In the treatment of acute DVT study, incidence of major bleeding from rivaroxaban was similar to warfarin (0.8% vs. 1.2%, p=0.21).[2]

- In thromboprophylaxis after total knee or total hip arthroplasty trials (RECORD trials), the incidence of major bleeding from rivaroxaban was similar to enoxaparin group (0.6% vs. 0.5% in total knee arthroplasty; 0.3% vs. 0.1% in total hip arthroplasty, p=0.18).4,6

Non-hemorrhagic adverse reactions include:

- *Central nervous system:* Fatigue (1%), syncope (1%)
- *Dermatologic:* Wound secretion (3%), pruritus (2%), skin blister (1%)
- *Gastrointestinal:* Nausea (1% to 3%), abdominal pain (2%), dyspepsia (1%), toothache (1%)
- *Genitourinary:* Urinary tract infection (1%)
- *Hepatic:* Increased serum transaminases (>3 x ULN: 2%)
- *Neuromuscular & skeletal:* Back pain (4%), limb pain (2%), osteoarthritis (2%), muscle spasm (1%)

Respiratory: Oropharyngeal pain (1%), sinusitis (1%)
<1% (Limited to important or life-threatening): Agranulocytosis, cholestasis, decreased hemoglobin (≥2 g/dL), dysuria, ecchymoses, epidural hematoma, hemiparesis, hemophthalmos, hepatitis, hepatic injury, hypermenorrhea, hypersensitivity, hypotension, increased amylase, increased blood urea nitrogen, increased lactate dehydrogenase, increased serum alkaline phosphatase, increased serum creatinine, increased serum lipase, intracranial hemorrhage, jaundice, retroperitoneal hemorrhage, Stevens-Johnson syndrome, subdural hematoma, tachycardia, thrombocytopenia (Data from postmarketing experience

approved by FDA)(<100,000/mm^3 or <50% baseline)

8. Drug interaction

Rivaroxaban is metabolized by CYP3A4, CYP2J2, and active renal secretion mediated by P-gp and breast cancer resistance protein.

Co-administration with strong inhibitors of both CYP3A4 and P-gp, such as azole antimycotics (ketoconazole, itraconazole), the HIV protease inhibitor (lopinavir/ritonavir, ritonavir, indinavir/ritonavir), or conivaptan, led to significant increased exposure and pharmacodynamic effects.[22,23] Strong inhibitors of one or the other or moderate inhibitors of both pathways have less effect on pharmacokinetics and pharmacodynamics.

Co-administration with strong inducers of both CYP3A4 and P-gp (carbamazepine, phenytoin, rifampin, St. John's wort) led to decreases in pharmacokinetic and pharmacodynamic effects and should be avoided.

9. Mechanism of action

Direct Factor Xa inhibitor. It inhibits free, prothrombinase-associated and clot-associated Factor Xa.[24] Factor Xa is responsible for converting prothrombin (Factor II) to thrombin (Factor IIa).

10. Monitoring parameter

Routine coagulation monitoring is not required due to predictable pharmacokinetics and pharmacodynamics profiles. However, in cases of immediate assessment of anticoagulation, such as prior to urgent surgery, it may be useful. Prothrombin time (Neoplastin) or antifactor Xa activity may be used to detect the presence of rivaroxaban. Neither is intended to be used for dosage adjustment. However, variability exists among PT assays and even more so when converted to INR. Therefore, antifactor Xa activity measurement is the preferred test.[25-28]

11. Pregnancy

Category C. There are no adequate or well-controlled studies in pregnant women, and dosing for pregnant women has not been established. There is potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible.[8]

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity with increased resorptions, decreased number of live fetuses and decreased fetal body weight in animals.

12. Lactation

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. A decision should be made whether to discontinue nursing or discontinue rivaroxaban.[8]

13. Pharmacokinetic and pharmacodynamics[8]

- *Absolute bioavailability:* 80-100%
- *Time to peak plasma concentration:* 2-4 hours
- *Time to maximal Factor Xa inhibition:* 1-4 hours
- *Apparent half-life:* 5-13 hours[22].
- *Volume of distribution:* 50 liters
- *Metabolism:* CYPP450 3A4, CYP2J2, P-gp and breast cancer resistance protein

Excretion: One third of a drug is excreted directly by the kidneys as unchanged, active drug. Two-thirds of a drug undergoes hepatic metabolic degradation and is eliminated by the kidneys and hepatobiliary route.

Plasma protein binding: 92-95%, thus not dialyzable.

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Received: 03/09/2015
Accepted: 03/27/2015
Reviewers: Scott Shurmur MD
Published electronically: 4/15/2015
Conflict of Interest Disclosures: None

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